AN APPROACH TO THE TOTAL SYNTHESIS OF (±)-NAPHTHYRIDINOMYCIN A

Thesis by

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To Mom and Dad

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A special thanks goes to Pete Koelsch for his friendship and for saving my life on Mt. Waterman on February 9, 1980.

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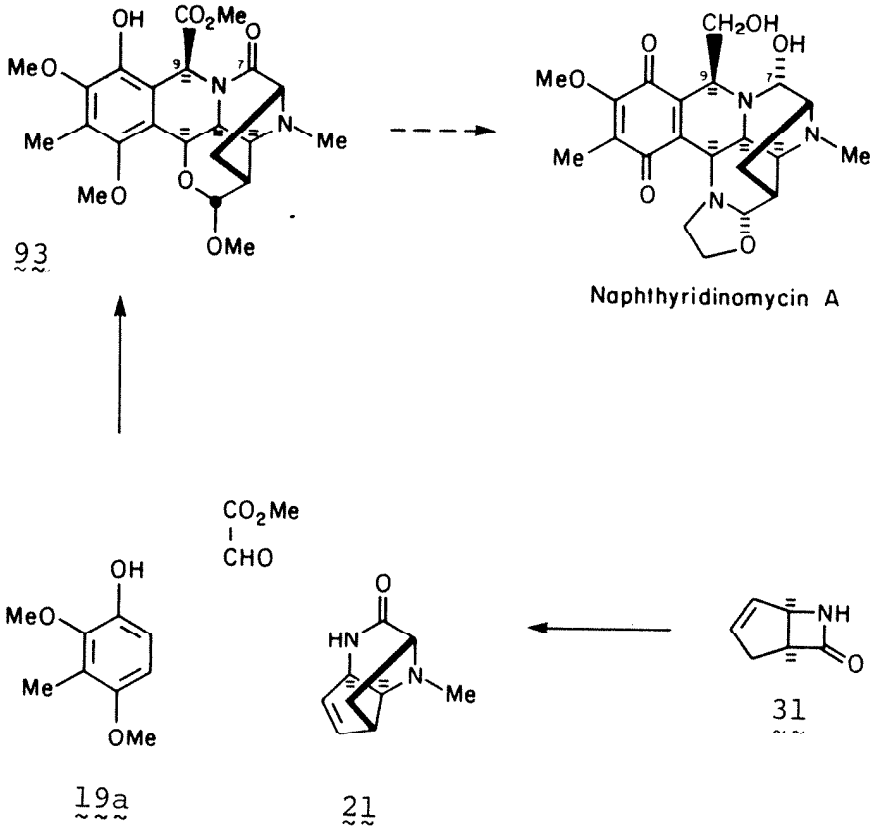
ABSTRACT

An approach to the total synthesis of the quinone antibiotic (±)-naphthyridinomycin A is described. This research has thus far culminated in the preparation of the advanced, pentacyclic intermediate 93. The structure of phenol 93 was secured by an X-ray crystallographic study of its benzoate ester. Intermediate 93 was constructed from tricyclic lactam 21, phenol 19a and methyl glyoxalate, employing a stereoselective amidoalkylation reaction and an intramolecular Friedel-Crafts alkylation as key



transformations. With regard to the amidoalkylation step, several new methods for the generation of acylimmonium ions were developed in the course of model studies. The synthesis of tricyclic lactam 21 from the readily available bicyclic β-lactam 31 was accomplished via a 13-step sequence, which included several interesting intramolecular reactions.

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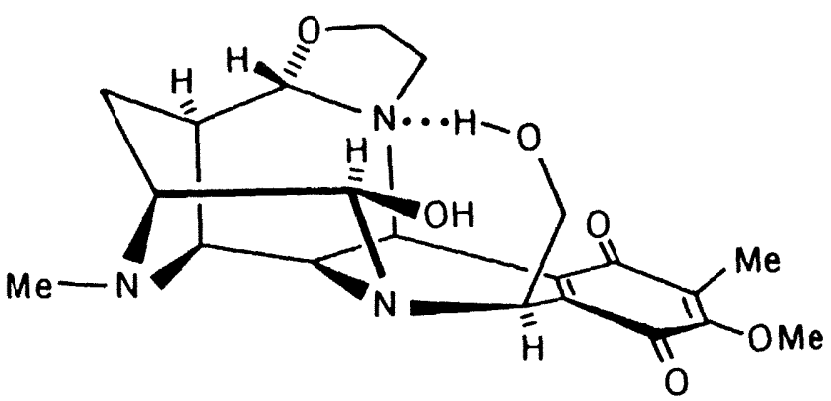
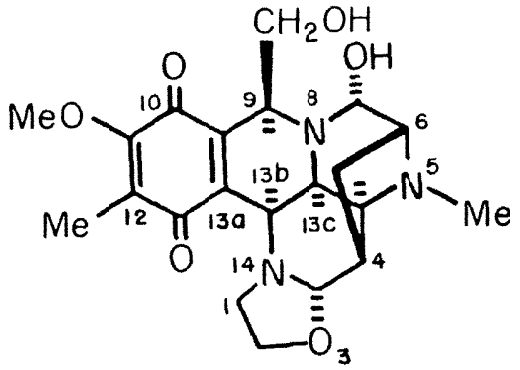
An Approach to the Total Synthesis of (±)-Naphthyridinomycin A

I. Background and Retrosynthetic Analysis

The novel broad spectrum antibiotic naphthyridinomycin A (1, Figure 1)[1] was isolated in 1974 from Streptomyces NRRL 8034. The structure of this fascinating alkaloid was elucidated by X-ray crystallography.[1b,c] Presented in Figure 1 is a stereo-drawing of the conformation found in the X-ray crystal structure. A minor cogener, naphthyridinomycin B, has also been isolated, but has not been completely characterized.[1d] Naphthyridinomycin A belongs to a growing class of antibiotics which possess a common quinone nucleus, as well as other structural similarities. These include the mitomycins (e.g. mitomycin A, 2),[2] the saframycins A-C (3),[3] and the structurally less complex members mimosamycin (4),[4] mimocin (5)[5] and renierone (6).[6] This report addresses our progress toward the total synthesis of naphthyridinomycin A.

Biological studies reveal that naphthyridinomycin A is quite active against a wide variety of both gram-positive and gram-negative bacteria.[1a] Its primary mode of action in E. coli appears to be the inhibition of DNA synthesis, which occurs within a few minutes of exposure to low concentrations of the substance.





1

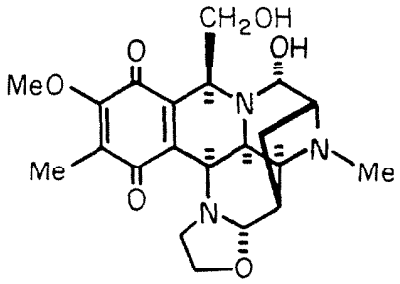
Naphthyridinomycin A

Streptomyces NRRL 8034

Structure: Brisse, Hanessian, 1974.

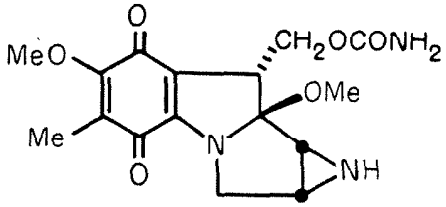
Figure 1

QUINONE ANTIBIOTICS



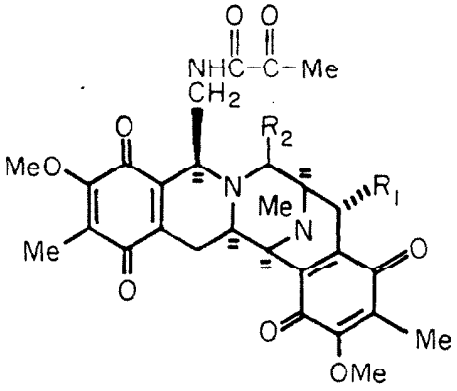
Naphthyridinomycin A

1



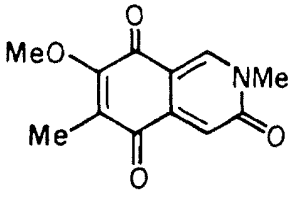
Mitomycin A

2



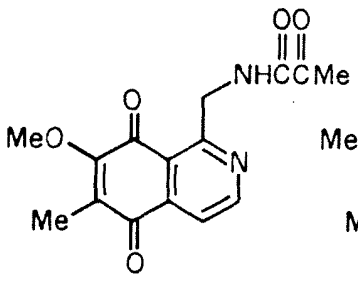
3

Saframycin		R_1	R_2
	A	H	CN
	B	H	H
	C	OMe	H



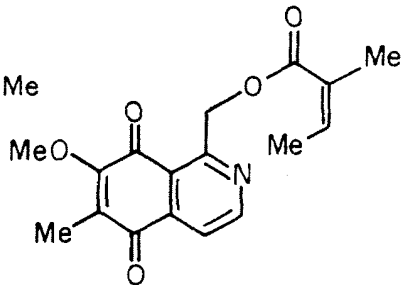
Mimosamycin

4



Mimocin

5



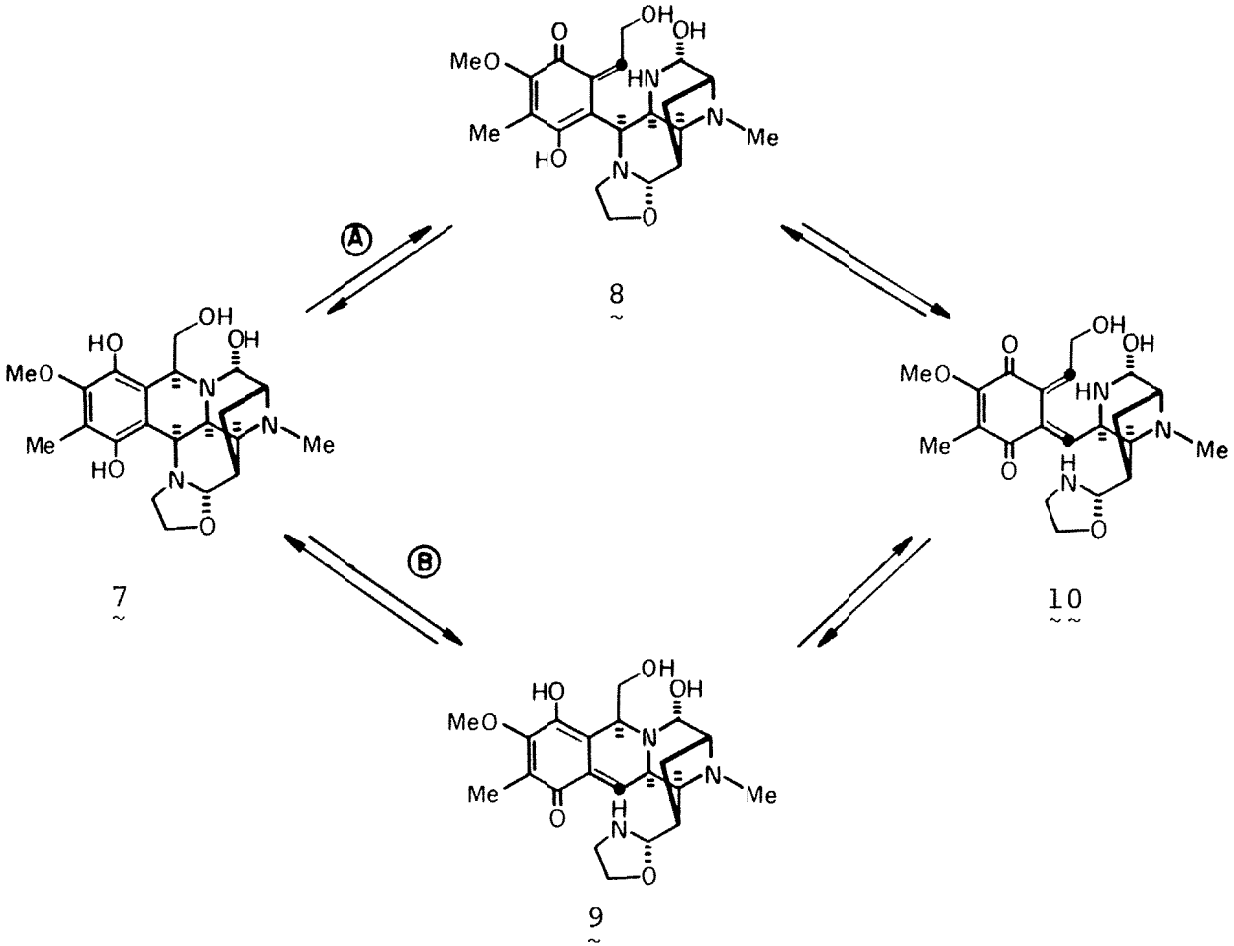
Renierone

6

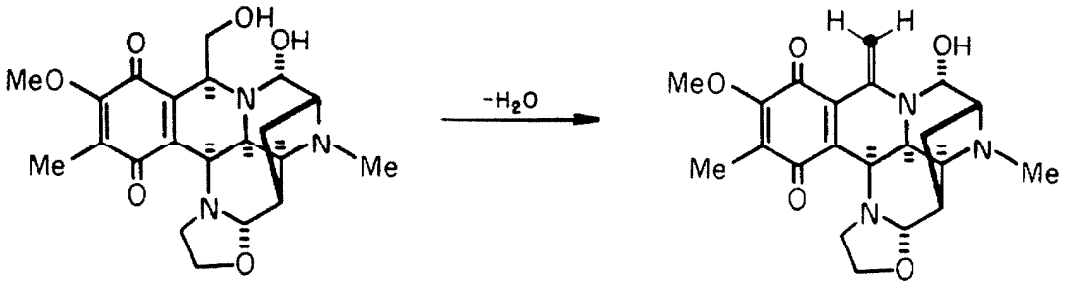
In this respect, naphthyridinomycin A is similar to mitomycin C.[7] However, unlike mitomycin C, naphthyridinomycin A does not promote the degradation of intracellular DNA.

With regard to its antibacterial activity, naphthyridinomycin A may be functioning as a bioreductive alkylating agent as proposed by Moore[8] (Scheme I). In vivo reduction of the quinone nucleus to afford hydroquinone 7, followed by 1,4-elimination via pathway A or B would generate quinone methide 8 or 9. These intermediates have been suggested to serve as reactive bioalkylating agents at the indicated carbons. Indeed, naphthyridinomycin A may act as a double alkylating agent which could cross-link two biopolymers by exploiting these quinone methides sequentially or simultaneously via the bis-quinone methide 10. Quinone methides 8 and 9 may also be useful intermediates for key bond constructions in the total synthesis of 1 (vide infra).

Scheme I



An alternative potential biomechanism is illustrated in equation 1. Enzyme-promoted elimination of water could provide vinyl quinone 11, which should also be a potent bioalkylating agent.



(1)

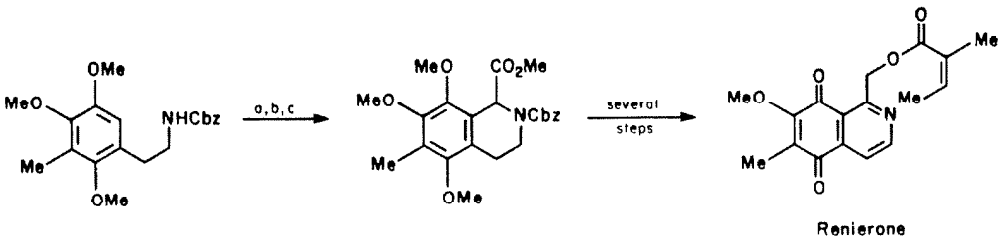
1 11

All of the quinone antibiotics presented previously (1-6) are unified in that one or both of the mechanisms discussed above may be responsible for their biological activity;[8] that is, they all possess latent leaving groups α- and β- to the quinone nucleus which could be used in the formation of quinone methides and vinyl quinones respectively. This analogy suggests that naphthyridinomycin A may be found to possess antitumor activity, as has been established for the mitomycins[2,7] and the saframycins.[9]

In yet another biomechanistic proposal, the aminal functions at positions 3a and 7 of naphthyridinomycin A

have been suggested to serve as precursors to immonium ions which would alkylate basic sites on DNA. This notion finds precedent in related studies on the aminal containing antibiotic anthramycin.[10]

Synthetic efforts in this area have mainly been limited to the mitomycins,[2] culminating in the elegant total syntheses of several members of this family by Kishi.[11] A recent report by Danishefsky illustrates the application of an intramolecular amidoalkylation reaction to the synthesis of renierone (eq 2).[12] In addition, total syntheses of mimosamycin (4)[4] and mimocin (5)[5] have been achieved.



(2)

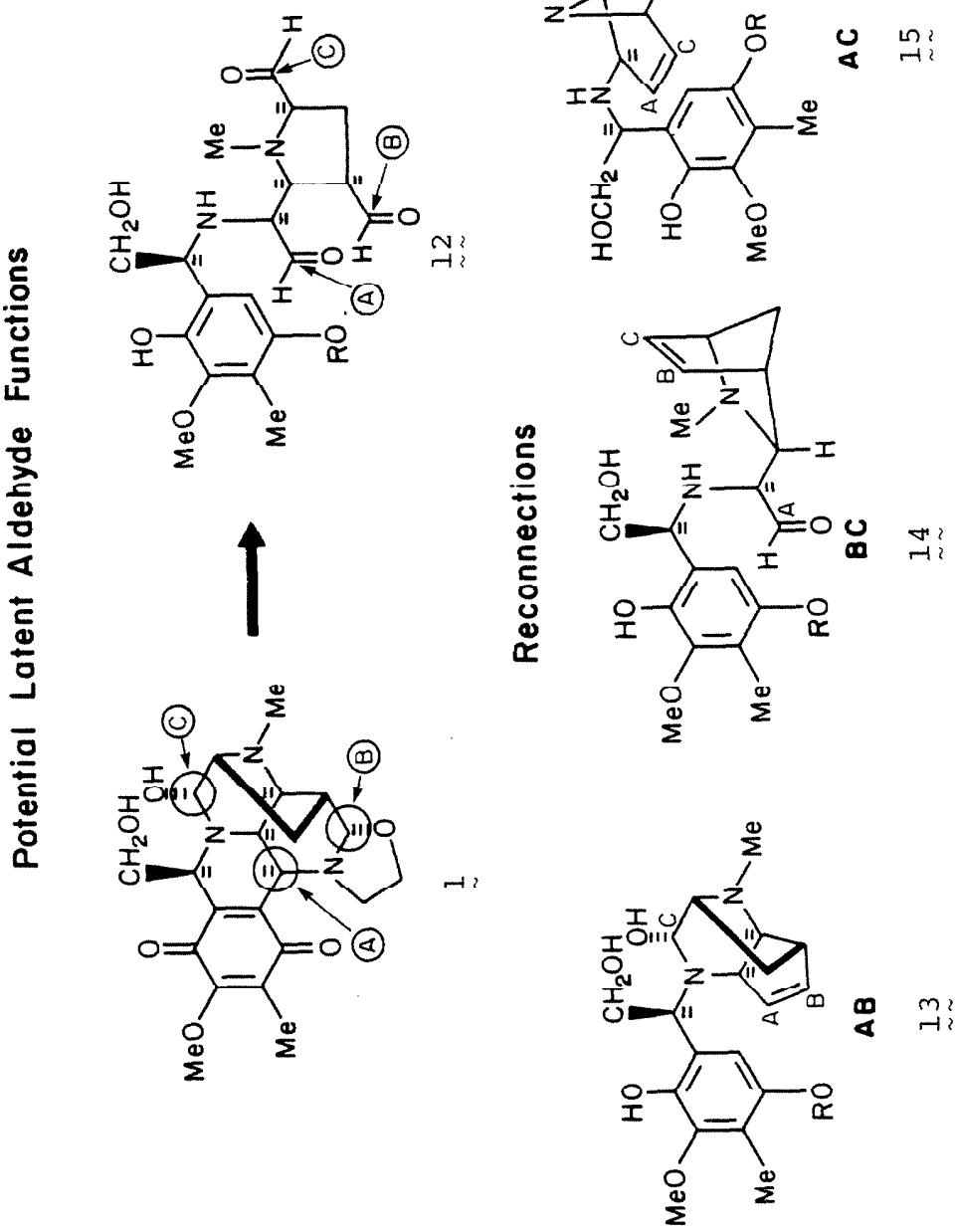
(a) $CHOCO_2H$, (b) $CHCl_2CO_2H$, (C) CH_2N_2.

Examination of the structure of naphthyridinomycin A (Figure 1) reveals that it possesses eight chiral centers, an abundance of heteroatoms, and a diverse array

of potentially sensitive functional groups. An additional problem associated with designing a synthesis of this molecule is that no chemistry has been reported on the intact antibiotic. These factors, as well as its biological activity, make naphthyridinomycin A a very challenging and worthwhile target for total synthesis.

In deriving a synthetic plan, we have assumed that the desired stereochemistry at positions 3a and 7 is thermodynamically favored and can be attained by facile equilibration. Furthermore, the intramolecular hydrogen bond between the 9-hydroxymethyl group and the 14-nitrogen atom indicated in the crystal structure (Figure 1), suggests that the stereochemistry at position 9 may be attained by base-catalyzed equilibration.

Initial retrosynthetic analysis reveals that naphthyridinomycin A possesses three latent aldehyde functions labeled A, B and C (Figure 2). The latent aldehydes B and C are readily derived via hydrolysis of the hemiaminal and oxazolidine groups, respectively, whereas aldehyde A results from a retro-Friedel-Crafts disconnection. This transform affords the pyrrolidine trialdehyde 12. Cyclic olefins can serve as very convenient protecting groups for polycarbonyl compounds,



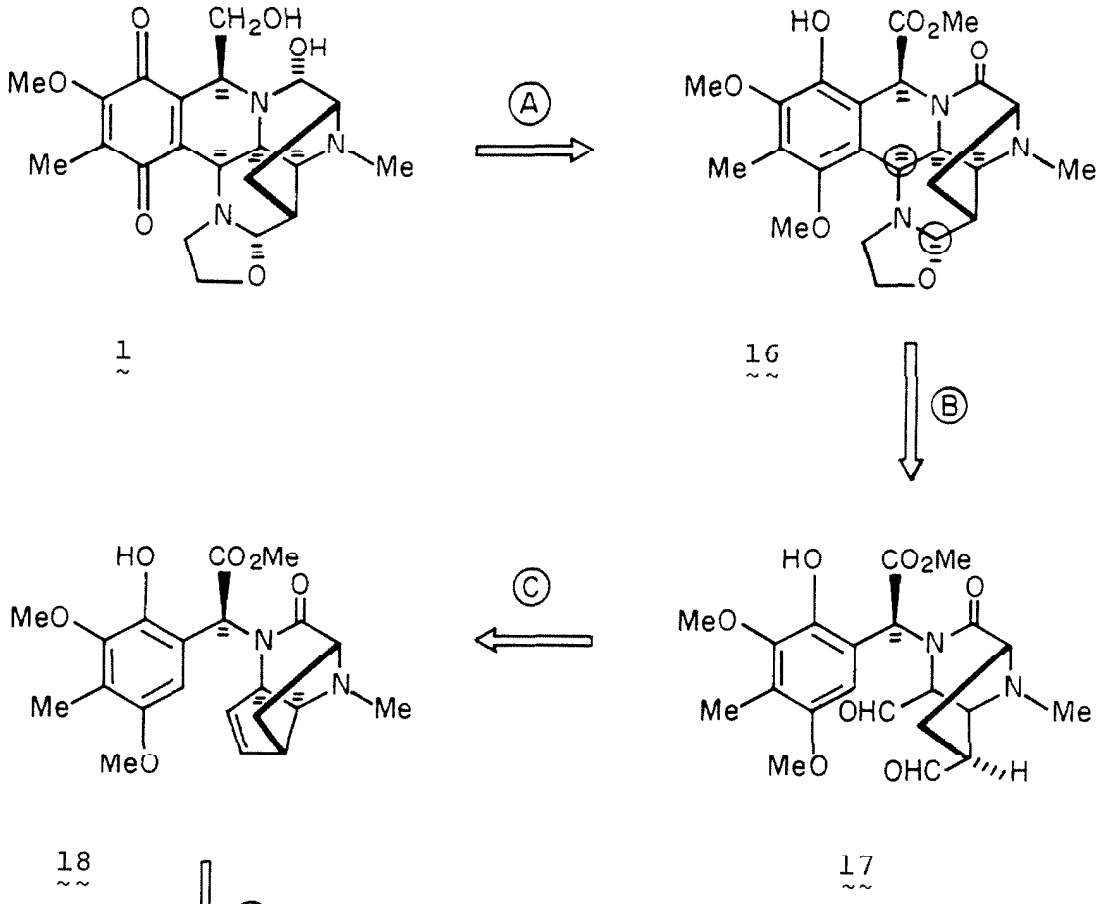
1 12 13 14 15

Figure 2

maintaining these sensitive functionalities in a state of low reactivity until they are revealed by an oxidative cleavage reaction.[13] Thus, reconnection of each dialdehyde pair to form cyclic olefins leads to three plausible intermediates: 13, 14 and 15. Evaluation of each of these synthons in terms of ease of preparation and viability of its ultimate conversion to the final product led to the selection of 13 as a subgoal for the synthesis project.

The overall strategy which was pursued is illustrated in Scheme II. To facilitate the proposed chemistry, we felt that the oxidation states of the 9-hydroxymethyl group, the 7-hemiaminal group and the quinone nucleus should be adjusted as indicated in transform A. Having a methoxycarbonyl group at position 9 would allow base promoted equilibration at this center, if necessary. Implicit in this transform was the assumption that the appropriate oxidation-reduction reactions could be performed towards the end of the synthesis to establish the required oxidation levels. As discussed previously, disconnection to dialdehyde 17 (transform B), followed by reconnection to form the tricyclic olefin (transform C), provides 18 as a subtarget. Intermediate 18 could then be derived from the amidoalkylation reaction[14,15] of phenol

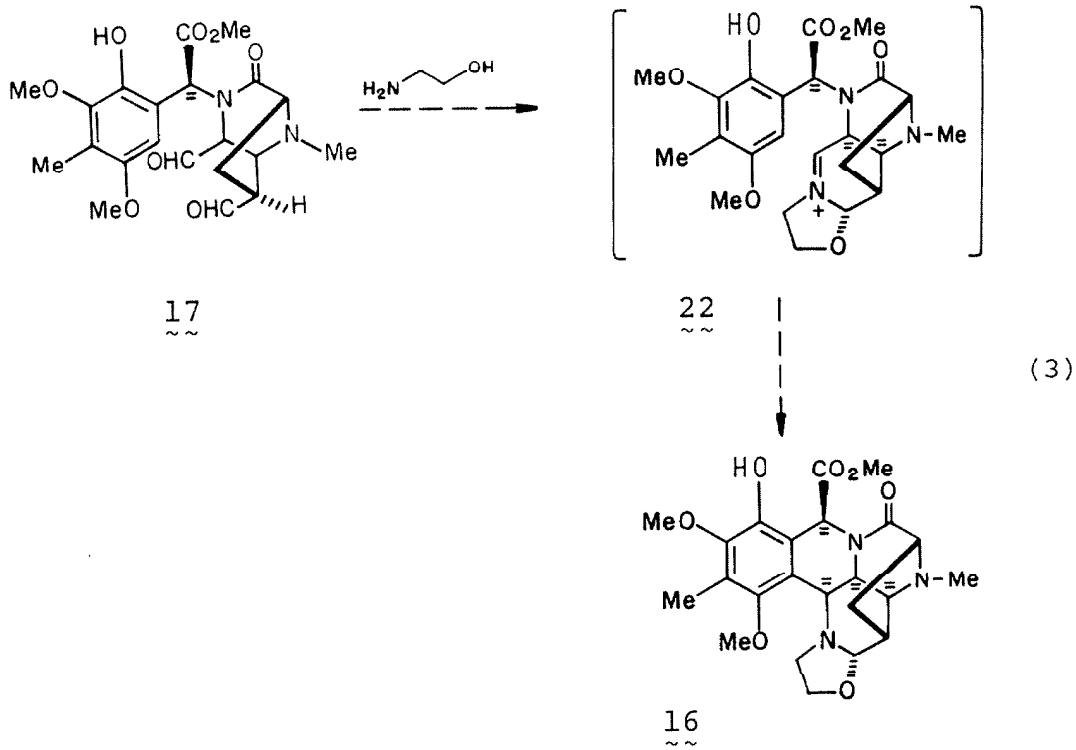
Scheme II



1 16 17 18 19a 20 21

19a and acylimmonium ion 20. We hoped to control both the regio- and stereochemical outcome of this reaction, such that 18 is formed in preference to the three other possible isomers. Phenol 19a is readily available and has been employed by Kishi for the synthesis of the mitomycins.[11,16] Acylimmonium ion 20 should be readily formed from the corresponding lactam 21 and methyl glyoxalate by a variety of methods. Thus, lactam 21 was chosen as the initial subgoal, and its preparation is described in part II of this report.

At this juncture, the transformation of dialdehyde 17 or its operational equivalent, to the hexacyclic



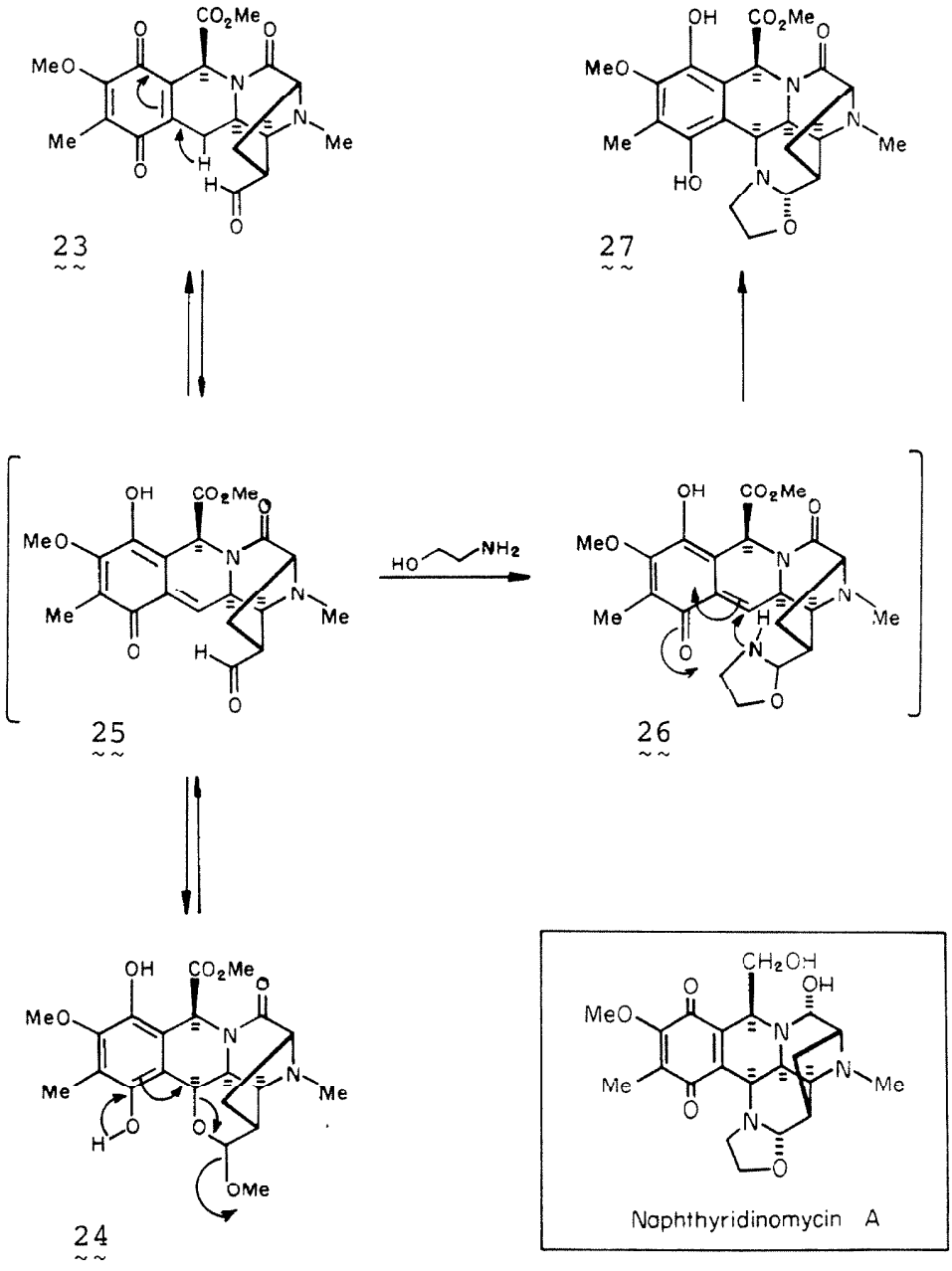
17 22 16 (3)

material 16, warrants further discussion. A very speculative solution to this problem is illustrated in equation 3. Reaction of 17 with 2-aminoethanol in the presence of acid should result in the formation of immonium ion 22, in equilibrium with other species. Intramolecular Mannich reaction of 22 would then construct the final carbon-carbon bond to afford 16.

In a somewhat less speculative plan, Friedel-Crafts cyclization of 17, or its equivalent, followed by subsequent straightforward transformations (not illustrated), would provide intermediates such as 23 and 24 (Scheme III). Note that 23 and 24 are at the same oxidation level and that each could serve as a precursor to quinone methide 25 via enolization and 1,4-elimination, respectively.[17,18] Incorporation of the oxazolidine ring would occur through the reaction of 25 with 2-aminoethanol to afford quinone methide 26, which should undergo a facile intramolecular Michael addition resulting in the hexacyclic structure 27.[17,18] Controlled reduction of the lactam and carbomethoxy functions, and oxidation of the aromatic ring would then afford naphthyridinomycin A.

Our initial attempt to apply this overall strategy to the synthesis of naphthyridinomycin A is the subject of this report.

Scheme III

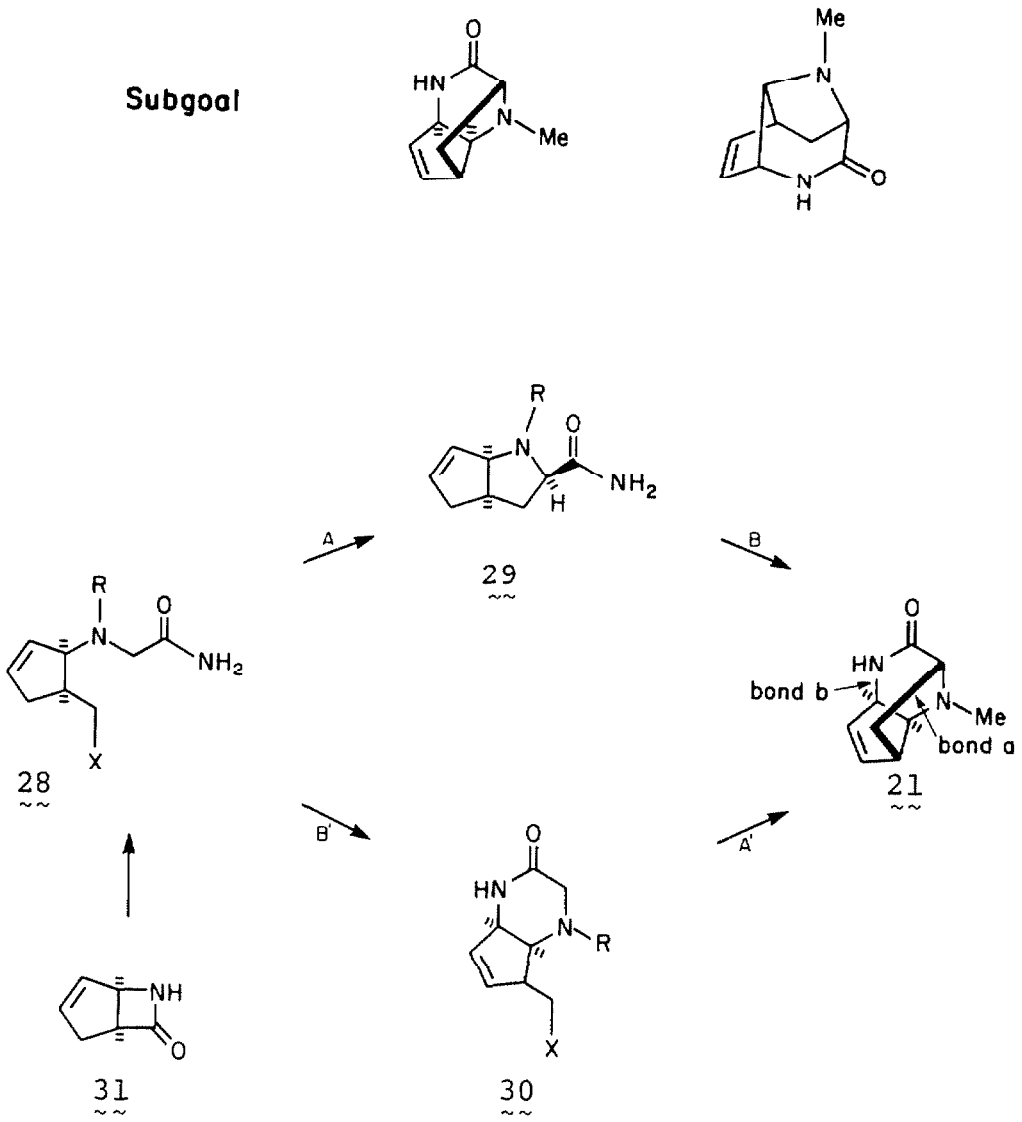

CO2Me
MeO
Me
N
Me
H
O
23
OH
HO
27
25
26
HO
NH2
24
OMe
CH2OH
Naphthyridinomycin A

II. The Synthesis of Tricyclic Lactam 21

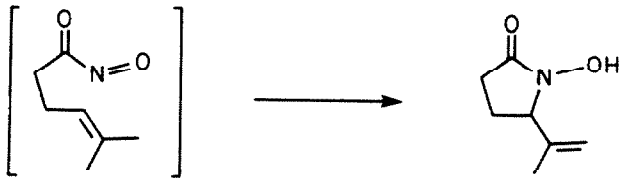
Introduction. As discussed in part I, the tricyclic lactam 21 serves as a major subgoal in the projected synthesis of naphthyridinomycin A. After considering the potential routes to 21, we focused on constructing bonds a and b as illustrated in Scheme IV. We felt that bond a could be formed in a straightforward manner via an intramolecular alkylation (reactions A, A'). The construction of bond b requires the cyclization of the carboxamide group onto the olefin, with migration of the double bond (reactions B, B'). This analysis suggested two complementary approaches to 21 which differ in the order of construction of bonds a and b, i.e. reaction sequences AB and B'A'. Both approaches required the preparation of monocyclic intermediate 28 or its equivalent. We felt that 28 could be efficiently prepared from the bicyclic β-lactam 31, which in turn is readily available via the [2+2] cycloaddition of chlorosulfonyl isocyanate and cyclopentadiene.[19] This stereospecific cycloaddition serves to establish two of the four asymmetric centers required for the synthesis of 21.

There are several methods which could be employed

Scheme IV

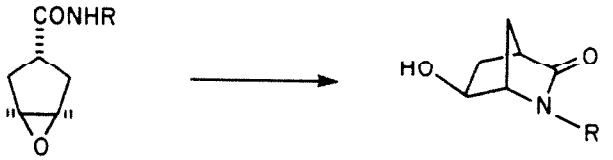

Subgoal
Me
N
HN
O
N
H
Me
R
N
O
NH2
H
29
A
B
R
N
O
NH2
X
28
bond b
HN
O
N
Me
bond a
21
B'
A'
HN
O
N
R
X
30
NH
O
31

to construct bond b in the desired manner: the intramolecular ene reaction of an acylnitroso intermediate (eq 4),[20] the base-promoted cyclization of an epoxy amide (eq 5),[21] and the radical-chain cyclization of an olefinic N-chloroamide (eq 6).[22] The latter two methods must be coupled with an elimination step (dehydration and dehydrochlorination, respectively) in order to generate the desired olefin.



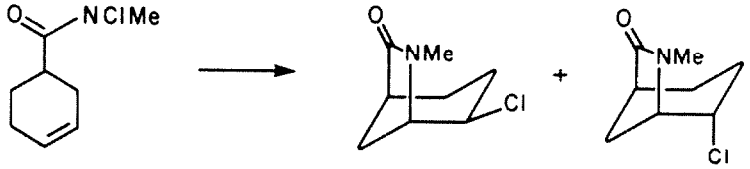
(4)

(ref 20)



(5)

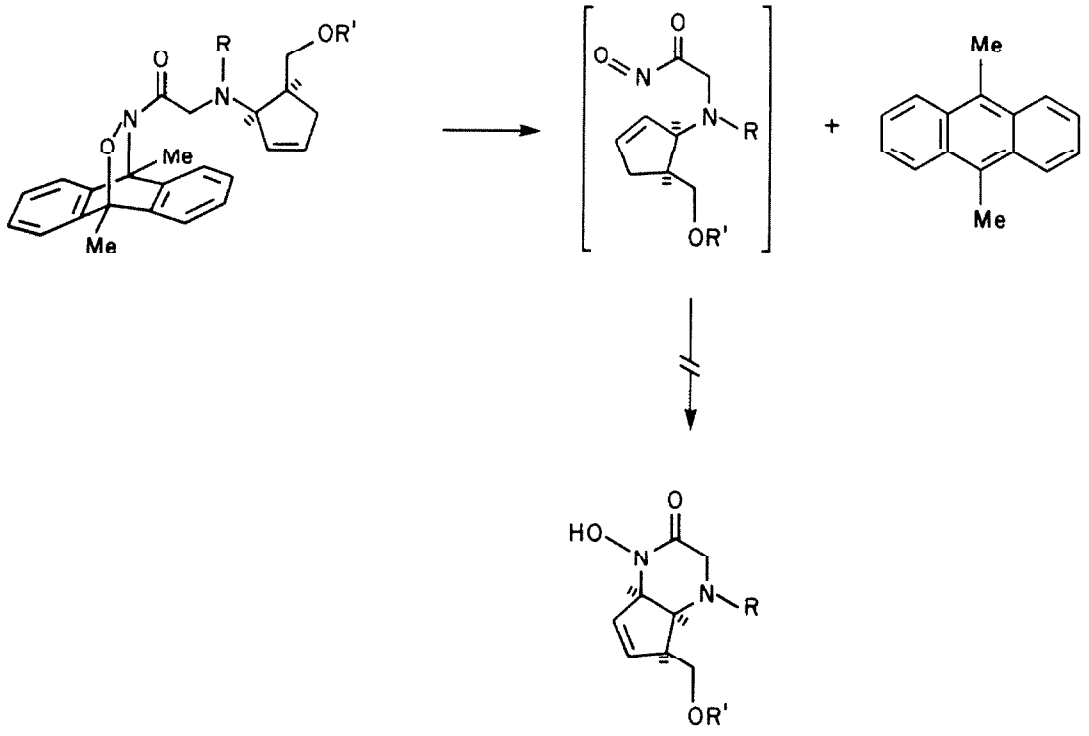
(ref 21)



(6)

(ref 22)

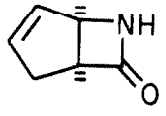
Initial studies aimed at the synthesis of 21 via reaction sequence B'A', employing the intramolecular nitroso-ene reaction outlined in equation 7, were unsuccessful. The remainder of this chapter will describe a successful approach to 21 which follows the reaction sequence AB.



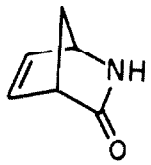
(7)

Results and Discussion. Bicyclic β-lactam 31, the starting material for our journey towards 21, had been prepared by Malpass[19] in 34% yield, employing the [2+2] cycloaddition of chlorosulfonyl isocyanate[23] and cyclopentadiene. After greatly improving this procedure, β-lactam 31 could be readily obtained in quantities

approaching one mole. Thus, reaction of chlorosulfonyl isocyanate[23] and cyclopentadiene in ether between -16°C and -24°C, followed by reductive hydrolysis of the intermediate N-chlorosulfonyl β-lactam (Na_2SO_3, K_2HPO_4, 0°C),[24] afforded 31 in 50-65% yield.[25] This reaction must be carried out with careful regard to the solution temperature, since higher temperatures resulted in mixtures of 31 and the rearranged lactam 32.[19]



31

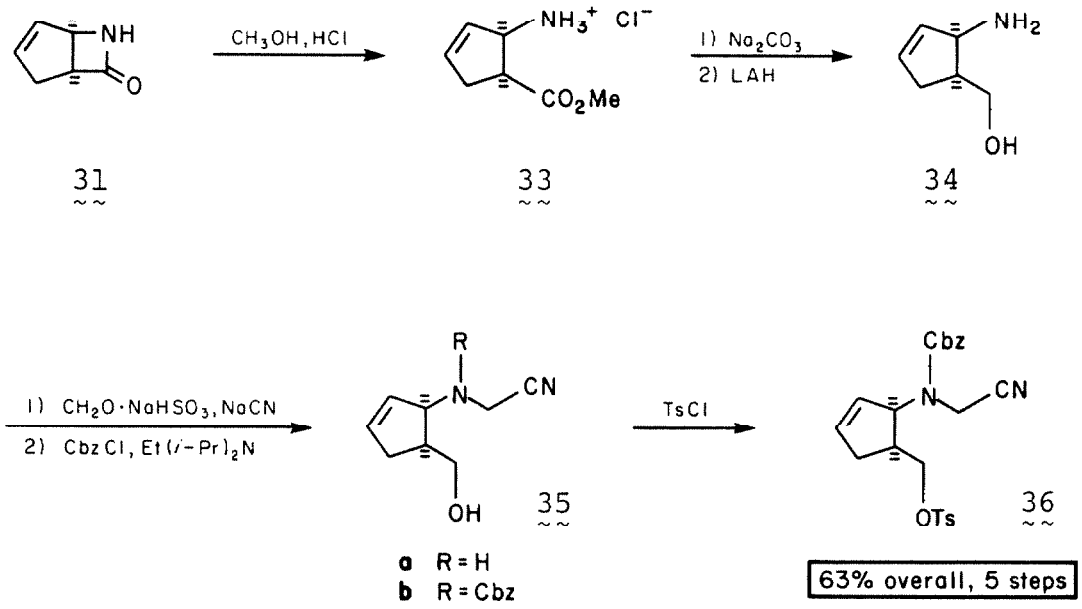


32

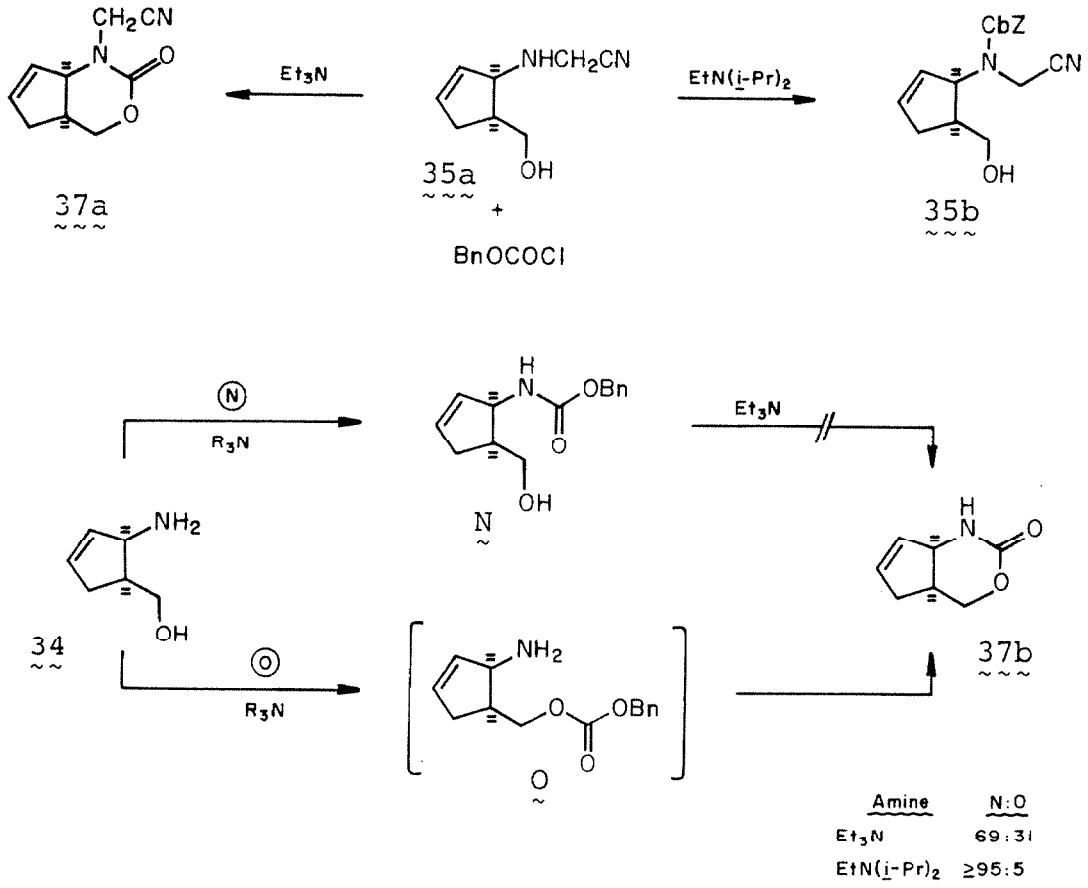
The conversion of bicyclic β-lactam 31 to nitrile-tosylate 36 is outlined in Scheme V. Treatment of 31 with methanolic hydrochloric acid afforded the β-amino ester hydrochloride 33 in 90% yield. The β-amino ester obtained upon freeing the hydrochloride 33 with aqueous sodium carbonate was reduced with lithium aluminum hydride to give the amino alcohol 34 in 80-89% yield. This sequence could be carried out on a large scale (0.84 mol) without purification at the intermediate stages to provide amino alcohol 34 in 89% overall yield from β-lactam 31. Cyanomethylation[26] of 34 ($CH_2O \cdot NaHSO_3$,

NaCN), followed by acylation with benzyloxycarbonyl chloride (CbzCl) in the presence of ethyldiisopropylamine afforded 35b in 86% yield. Formation of the corresponding tosylate 36 (TsCl, pyridine) proceeded in 84% yield. For large scale preparation (0.7 mol), the sequence from amino alcohol 34 to nitrile-tosylate 36 was most conveniently carried out without purification of the intermediates in 71% overall yield.

Scheme V



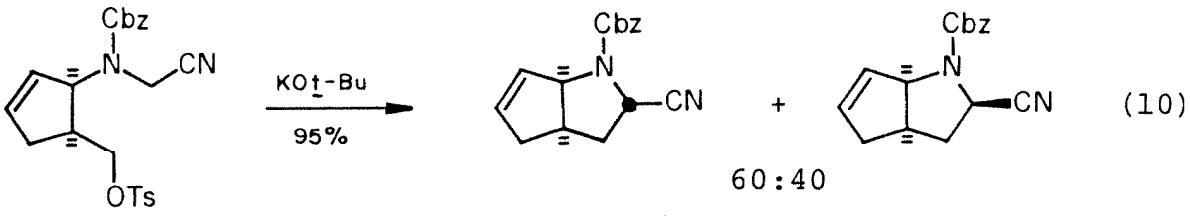
Inadvertently, we found that the reaction of amino alcohol 35a with CbzCl was highly dependent on the tertiary amine base employed. Whereas α-amido nitrile 35b was formed in high yield when the acylation was carried out in the presence of ethyldiisopropylamine, cyclic carbamate 37a was the major product (along with lesser amounts of 35b) when triethylamine was employed as the acid scavenger (eq 8). This same effect was noted in the acylation of amino alcohol 34 with CbzCl (eq 9). The kinetic acylation of these amino alcohols (illustrated for 34, eq 9) can occur on nitrogen (pathway N) to afford carbamate N, or on oxygen (pathway O) to afford carbonate O. Either of these intermediates could cyclize with loss of benzyl alcohol to give carbamate 37b. However, it was demonstrated that carbamate N does not cyclize to afford 37b upon treatment with triethylamine. Thus, we propose that 37b is formed via carbonate O. These observations suggest that the tertiary amine may be playing a role other than merely that of an acid scavenger. We feel that the increased propensity for acylation on oxygen in the presence of triethylamine results from the intermediacy of the acylammonium ion $CbzNEt_3^+ Cl^-$. Presumably, the formation of such an acylammonium ion intermediate



with ethyldiisopropylamine is precluded on steric grounds, and thus acylation occurs on nitrogen through direct reaction with CbzCl. The origin of the different kinetic selectivity for reaction on nitrogen versus oxygen exhibited by CbzCl and $CbzNEt_3^+ Cl^-$ remains obscure, and the generality of these observations have yet to be explored.

The next stage of the proposed synthesis was the intramolecular alkylation of nitrile-tosylate 36 to

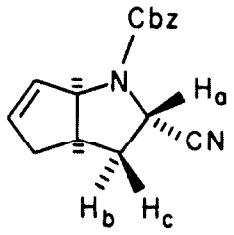
construct bond a (Scheme IV). This was accomplished by reaction of 36 with potassium t-butoxide to provide a 60:40 ratio of stereoisomeric bicyclic nitriles, 38 and 39 (eq 10). A priori, it was anticipated that little stereoselection would result from this alkylation process; however, it had been optimistically predicted that the diastereomeric nitriles could be resolved by chromatographic techniques. In the event, large scale separation of this isomeric mixture was readily achieved on the Water's Associates "Prep 500" high pressure liquid chromatograph[27] to afford bicyclic nitriles 38 and 39 in 57.5% and 37.5% yields, respectively.



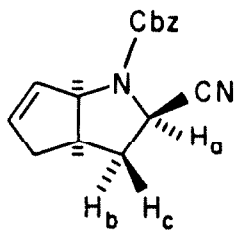
36 38 39

The stereochemical assignments of 38 and 39 were initially inferred by the base-catalyzed equilibration of the individual diastereomeric nitriles. In these experiments both 38 and 39 afforded a 59:41 ratio of 38:39 upon treatment with a catalytic amount of

potassium t-butoxide. Thus, it appears that the diastereomer ratio obtained in the alkylation process is thermodynamically controlled. The stereochemistry denoted in structure 38 was assigned to the major equilibrium isomer based upon straightforward consideration of non-bonded interactions. This assignment was consistent with the observed spectral data (500 MHz ^{1}H NMR), as well as by subsequent chemical investigations. Analysis of the



38



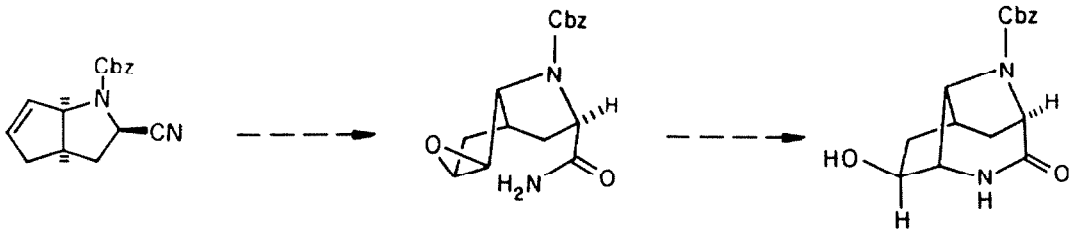
39

500 MHz ^{1}H NMR spectra of 38 and 39 was hampered by the presence of two (often overlapping) signals for almost every proton, due to the presence of two carbamate rotomers in nearly equal proportions. Assuming the pyrrolidine ring of isomer 38 exists in an envelope-type conformation, the dihedral angle between vicinal protons H_a and H_b approaches 90°, while that between H_a and H_c approaches 30°. This is consistent with the negligible coupling observed between H_a and H_b and the substantial coupling observed between H_a and H_c (J_{ac} = 8 Hz) for the major isomer.[28] In contrast, both of the corresponding

angles of 39 are suitable for coupling, which is consistent with the coupling constants observed for the minor isomer (J_{ab} = 8.5 Hz, J_{ac} = 4 Hz).[28]

Clearly, according to the strategy discussed in the introduction to this chapter, only bicyclic nitrile 39 is useful for the synthesis. Although we have not derived a completely satisfactory solution to this problem, it was gratifying to find that the undesired 38 could be equilibrated as described above on a preparative scale, in order to increase the overall yield of 39. In the event, cyclization of nitrile-tosylate 36, followed by separation of the isomers and base catalyzed equilibration of the undesired 38, afforded a 58% combined yield of the desired isomer 39. Indeed, this efficient recycle procedure could be repeated to obtain additional quantities of 39.

With the bicyclic nitrile 39 in hand, we addressed the task of constructing bond b (Scheme IV) to form the final ring of the tricyclic skeleton. We proposed that epoxidation of 39 from the sterically less encumbered face,[13b,29-31] followed by partial hydrolysis of the nitrile function, would provide epoxy amide 42, a substrate which is suitably disposed for ring closure (eq 11). It was anticipated that base treatment of 42 would result in intramolecular epoxide ring opening

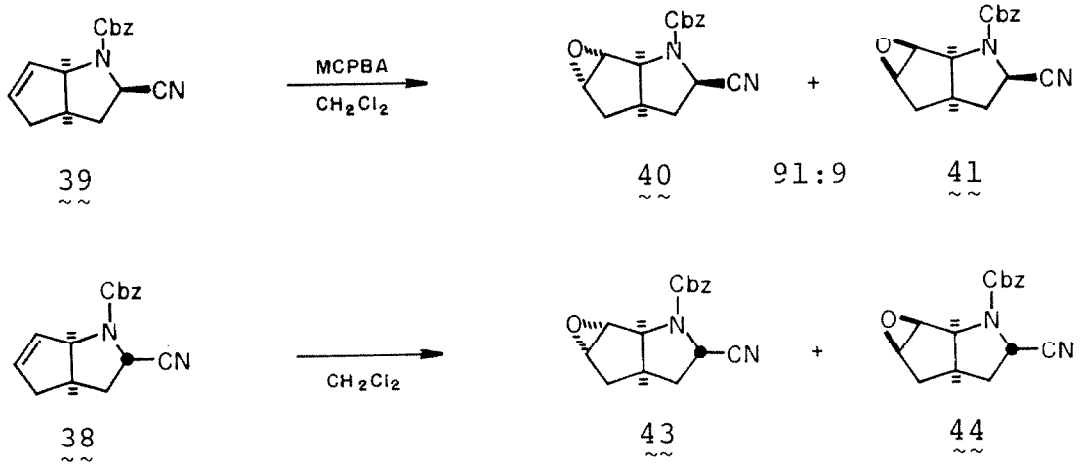


(11)

38 42 45

by the carboxamide function,[21] forming the desired six-membered lactam 45. In practice, the reaction of 39 with m-chloroperbenzoic acid afforded a 91:9 ratio of the two stereoisomeric epoxides, 40 and 41, which were isolated in yields of 88% and 8.7%, respectively (Scheme VI). Predictably, the epoxidation of stereo-

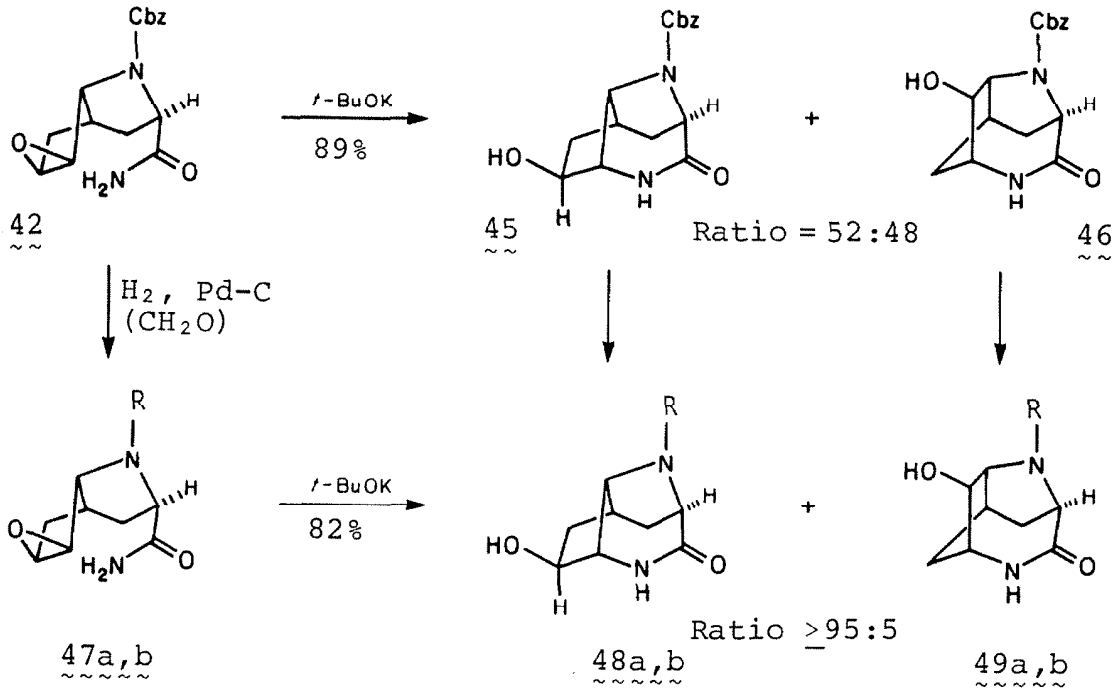
Scheme VI



isomer 38 proceeded in a less selective manner (MCPBA, 43:44 = 74:26; CF_3CO_3H, 43:44 = 68:32). This difference in stereoselectivity most likely results from a greater steric shielding of the β-face by the nitrile function in isomer 39, in addition to the dipole-dipole effect proposed by Henbest.[31]

Hydrolysis of nitrile 40 with basic hydrogen peroxide[32] gave the epoxy amide 42 in 91% yield (Scheme VII). A closer examination of structure 42 revealed that lactam ring formation could occur to afford the undesired seven-membered lactam 46 in addition to the desired six-membered lactam 45. Indeed, reaction of 42 with potassium t-butoxide resulted in a 52:48 mixture of isomeric lactams 45 and 46, which were separated by medium pressure liquid chromatography. This unfortunate situation could be improved in the following manner. Hydrogenolytic removal of the benzyloxycarbonyl group of 42 to yield secondary amine 47a (1 atm H_2, 5% Pd-C, CH_3OH), followed by the addition of aqueous formaldehyde and continued exposure to hydrogen, provided the corresponding N-methyl compound 47b in 95% yield.[33] Treatment of 47b with potassium t-butoxide afforded the six-membered lactam 48b (82%), nearly to the exclusion of isomer 49b.

Scheme VII



42 45 46

47a,b 48a,b 49a,b

a, R = H
b, R = Me

Lactams 48b and 49b were prepared independently from 45 and 46, respectively, via hydrogenolysis in the presence of formaldehyde. With a sample of 49b available for comparison, we were able to observe only traces of this material in the crude cyclization product resulting from base treatment of 47b (^{13}C and ^{1}H NMR, thin-layer chromatography).

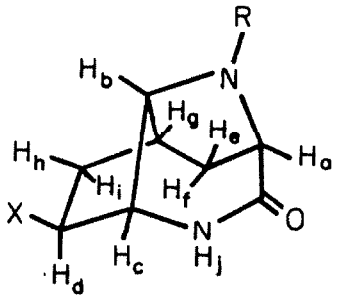
The secondary amine 47a underwent highly regioselective cyclization as well, to afford 48a. However,

the insolubility of 48a in all organic solvents except methanol and dimethyl sulfoxide made it difficult to isolate from the reaction mixture in pure form. Though more manageable than 48a, even 48b is only very sparingly soluble in chloroform and acetonitrile.

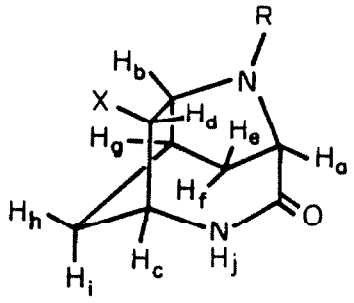
The reasons for low regioselectivity in the cyclization exhibited by 42 as compared to 47a,b remain obscure. Examination of molecular models suggests that $A^{1,3}$ strain[34] between the benzyloxycarbonyl group and the flanking hydrogens on the pyrrolidine ring may be more severe in the transition state which gives 45, compared to that which gives 46. Thus, the kinetic selectivity which generally favors the formation of six-membered over seven-membered rings may be perturbed to make the latter competitive.

The initial structural assignments for the isomers 45 and 46 were based on their 90 MHz ^{1}H NMR spectra with the aid of extensive proton decoupling experiments. These spectra contain several diagnostic coupling patterns. For example, the carbinol proton H_d of 45 appears as a doublet. This results from the orthogonal relationship between H_d and vicinal protons H_c and H_h, leaving only H_i at a proper angle for coupling (J_{di} = 4.5 Hz). In the case of 46 however, H_d appears as a

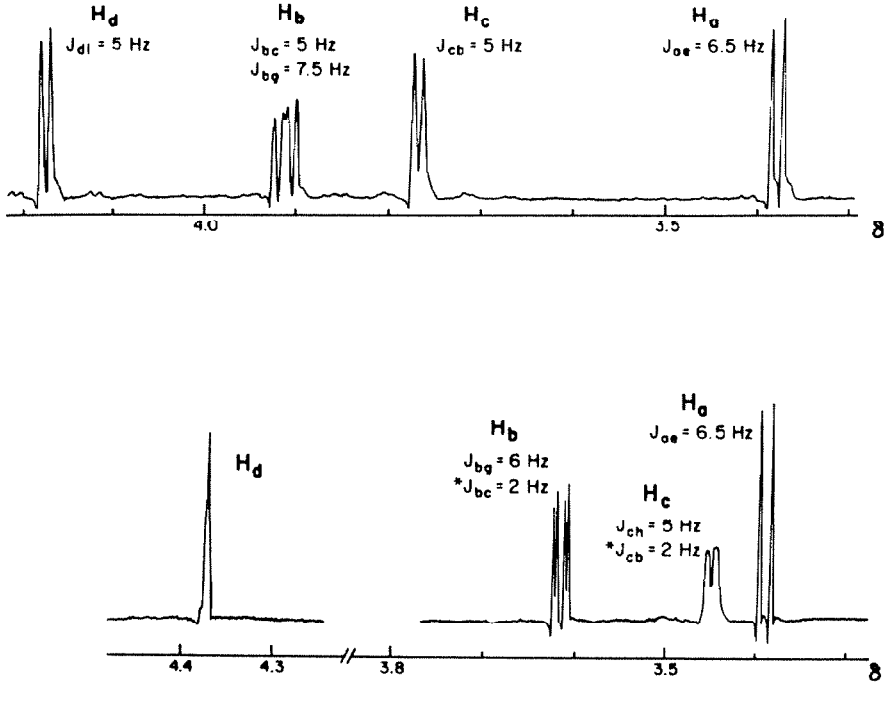
singlet, reflecting the orthogonal relationship between it and both of its vicinal neighbors H_b and H_c. In addition, H_b of isomer 45 possesses appropriate angles for coupling with both vicinal protons H_c and H_g (J_{bc} = 5 Hz, J_{bg} = 8 Hz), whereas H_b of isomer 46 is coupled with only one vicinal proton, H_g (J_{bg} = 6 Hz), due to a near orthogonal relationship with H_d.[28] Identical coupling patterns were evident in the 500 MHz ^1H NMR spectra of the N-methyl isomers 48b and 49b, which are compared over the critical δ 3.3-4.4 region in Figure 3. The relationship between the isomer pairs 46,47 and 48b,49b was further confirmed by the chemical correlations described previously. Finally, the spectral data for ketone 50 derived from 45 (CrO_3, pyridine),[35] and mesylate 51 derived from 48b, are entirely consistent with these assignments.

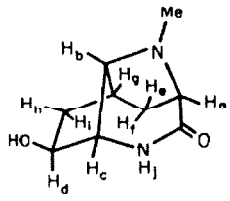


45, R = Cbz; X = OH
48b, R = Me; X = OH
50, R = Cbz; X, H_d = O
51, R = Me; X = OSO_2Me

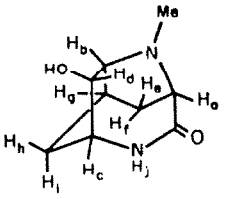


46, R = Cbz; X = OH
49b, R = Me; X = OH





48b



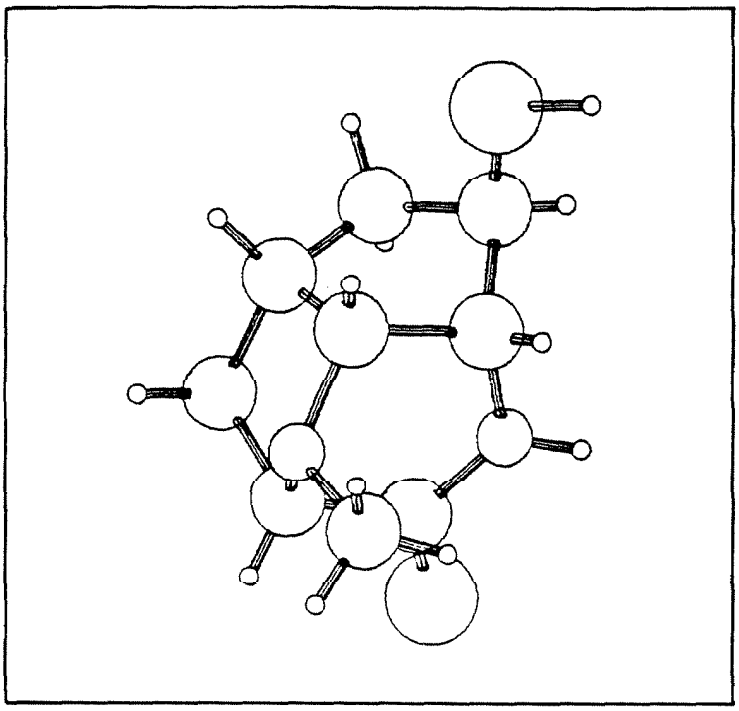
49b

*long range coupling

500 MHz ^{1}H NMR Spectra (D_2O)

Figure 3

Since 48b was such a pivotal intermediate in our projected synthesis, and to our knowledge, represented the first member of the 2,7-methano-1H-cyclopentapyrazine skeleton ever prepared, we resorted to X-ray crystallography to obtain unambiguous proof of its structure and stereochemistry. The results of the X-ray study, carried out by N. S. Mandel and G. S. Mandel at the Medical College of Wisconsin,[36] were completely consistent with our spectral analysis (Figure 4).



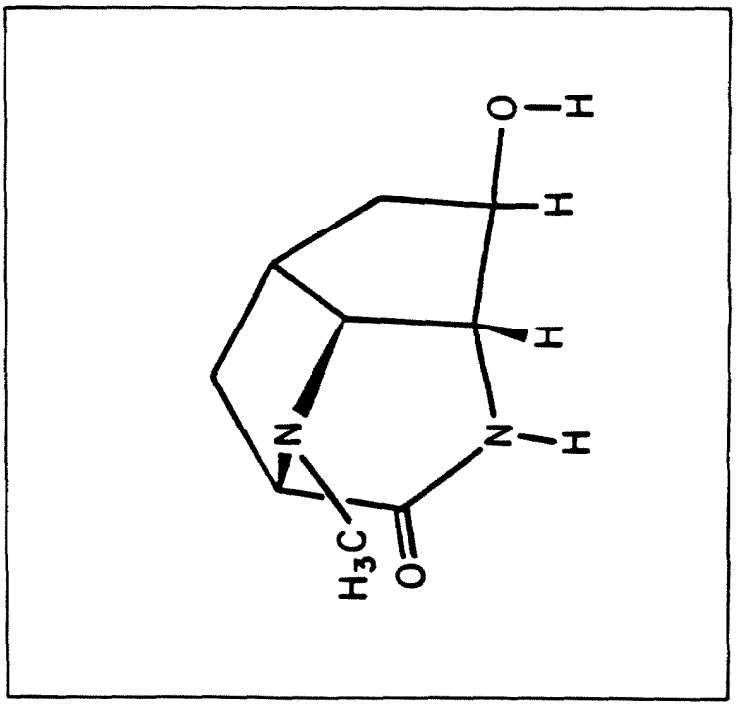
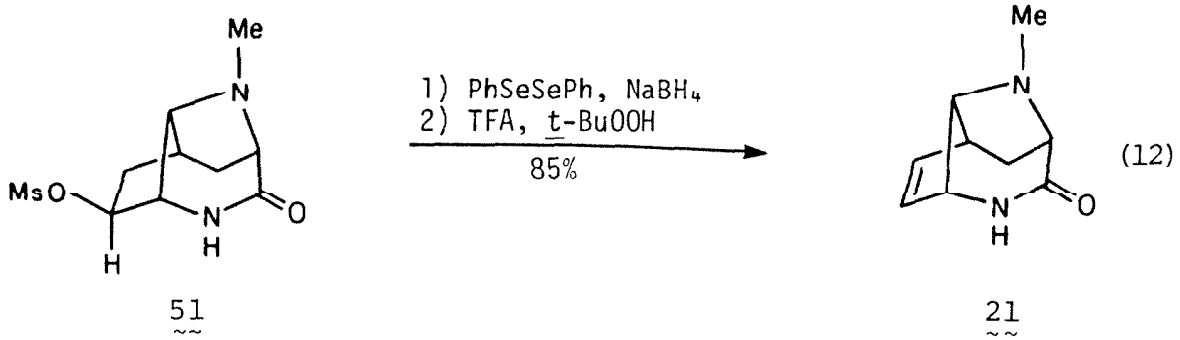


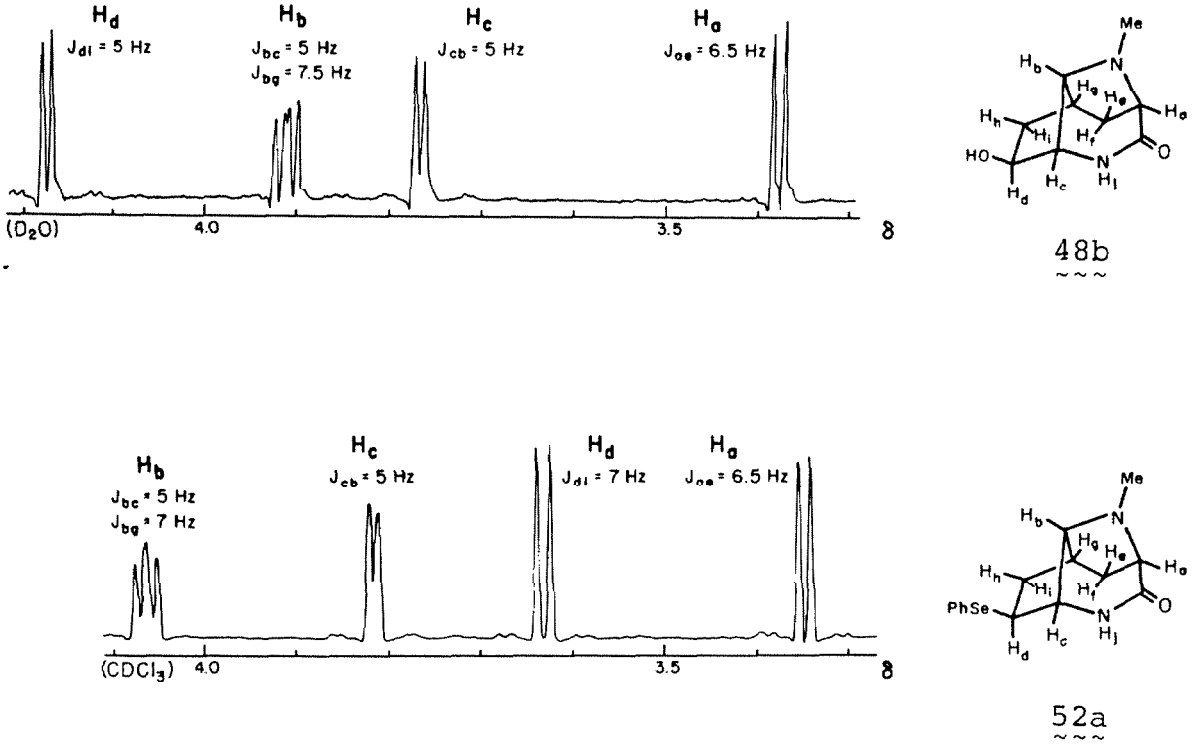
Figure 4. X-Ray Crystal Structure of 48b.

Having selectively constructed the desired tricyclic skeleton, it remained only to eliminate the elements of water from 48b to arrive at the desired subgoal 21. Attempted base promoted elimination of the corresponding mesylate 51 (CH_3SO_2Cl, Et_3N, 95%)[37] met with limited success. Treatment of 51 with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU)[38] in refluxing toluene led to the formation of product(s) which appeared to have DBU incorporated into the tricyclic skeleton. The reaction of 51 with potassium t-butoxide in dimethyl sulfoxide afforded a 15% yield of the desired olefin 21, along with a host of undesired byproducts. Alternatively, formation of the phenyl selenide (PhSeSePh, $NaBH_4$, 80°C, 97%)[39,40] followed by syn elimination of the corresponding selenoxide[40] (3 equiv t-BuOOH[41] on the trifluoroacetate salt, 88%) resulted in a high overall yield of olefin 21 (eq 12).



51 21 (12)

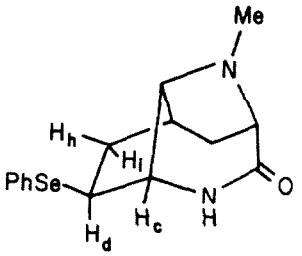
The ^{1}H NMR spectrum of the phenyl selenide intermediate revealed that its formation had occurred with retention of configuration! The coupling patterns are entirely consistent with the structure and stereochemistry indicated for 52a, in analogy to that of 45, 48b and 51 discussed above. This can be readily appreciated upon comparison of the 500 MHz ^{1}H NMR spectra of 48b and 52a in the region of δ 3.3-4.2 displayed in Figure 5. If



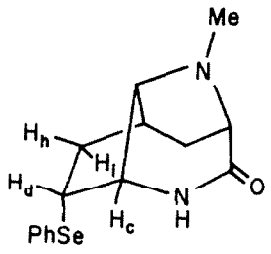
500 MHz ^{1}H NMR Spectra

Figure 5

the reaction had occurred with net inversion to afford 52b via an S_N2 process, molecular models suggest that H_d would be strongly coupled to H_c, H_h and H_i.[28] Only the latter coupling was noted in the 500 MHz ^1H NMR spectrum of the phenyl selenide ($J_{di} = 7$ Hz), which is in agreement with isomer 52a. An additional small coupling to H_d of approximately 2 Hz was noted in the 90 MHz ^1H NMR spectrum of phenyl selenide 52a. For reasons which remain unclear, this coupling was not observable at 500 MHz. Decoupling studies were carried out at 90 MHz in an attempt to determine the origin of this splitting, but were hampered by the close proximity of the critical proton signals at this field strength. However, the evidence tentatively suggests that H_h may be responsible for this coupling.[85]

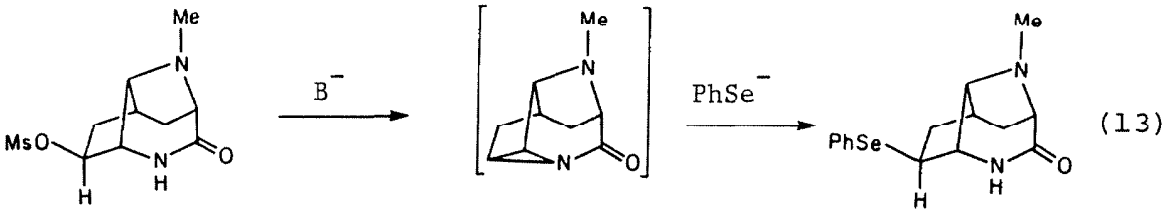


52a



52b

The above observations strongly implicate the intermediacy of acylaziridine 53 (eq 13),[42] which is formed by the base-promoted cyclization of 51, and then undergoes a highly regioselective nucleophilic cleavage by selenophenolate ion to afford 52a with net retention.[40,43,44] Indeed, the failure of the direct base-promoted elimination of mesylate 51 may have resulted from the partitioning of this highly strained and reactive intermediate (53) into undesired side pathways.

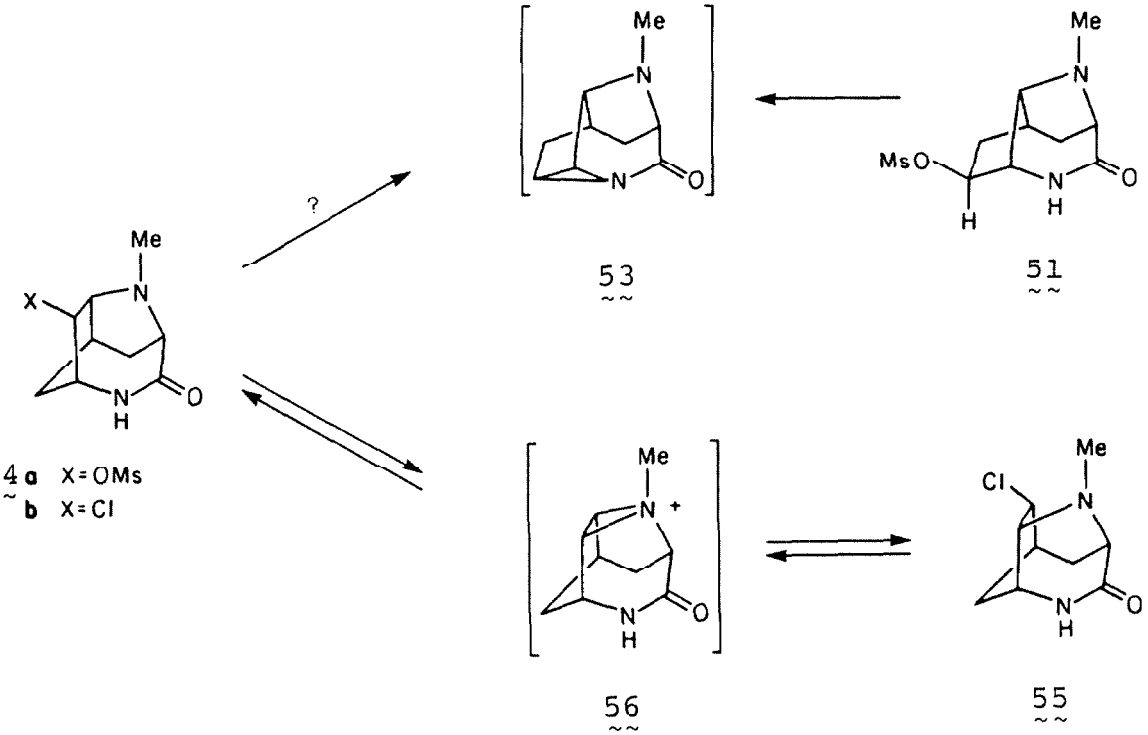


51 53 52a (13)

These results suggested that mesylate 54a, formed from the undesired seven-membered lactam 49b, might also serve as a precursor for acylaziridine 53 (Scheme VIII). In this manner, both ring systems could lead to the same phenyl selenide 52a. However, attempted formation of the mesylate 54a under standard conditions (CH_3SO_2Cl, Et_3N)[37] gave instead a mixture of chlorides

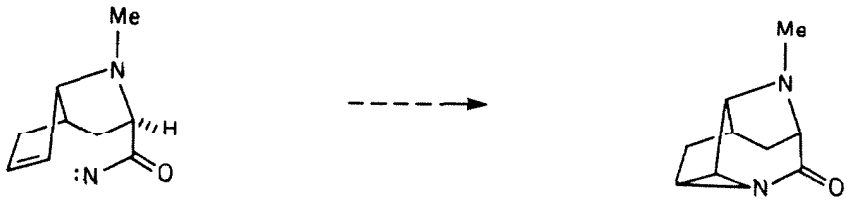
55 and 54b in a 1:1 ratio. This ratio was noted to change with time, approaching an equilibrium value of 55:54b = 3.6:1 after three days at room temperature. These observations are consistent with facile participation of the amino-function in the initially formed mesylate 54a to afford the aziridinium ion 56. Cleavage of this aziridinium ion by the more nucleophilic

Scheme VIII



chloride counterion at both possible sites would give chlorides 55 and 54b. Equilibration of these chlorides would then occur through the reversible formation and cleavage of aziridinium ion 56.[45-47] Thus, in order to further explore the notion that both ring systems could afford the same acylaziridine intermediate, parallel studies should be carried out on the mesylates derived from 45 and 46. Here, the benzyloxycarbonyl group precludes the sort of participation which thwarted the study described above.

An alternative approach to acylaziridine intermediate 53 might involve the intramolecular nitrene addition outlined in equation 14.[48] This route awaits experimental verification.

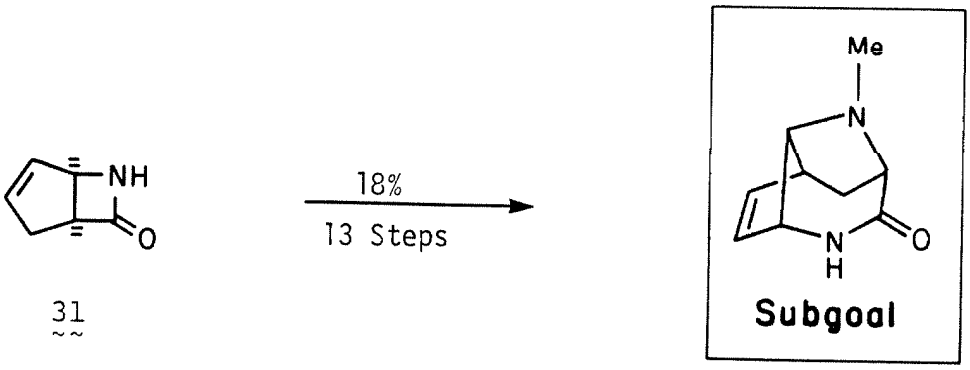


(14)

53

Summary. A synthesis of tricyclic lactam 21 was described, in an 18% overall yield (thirteen steps) from β-lactam 31 (including one recycle of bicyclic nitrile 38). Intermediate 21 possesses four of the eight asymmetric centers required for the synthesis of

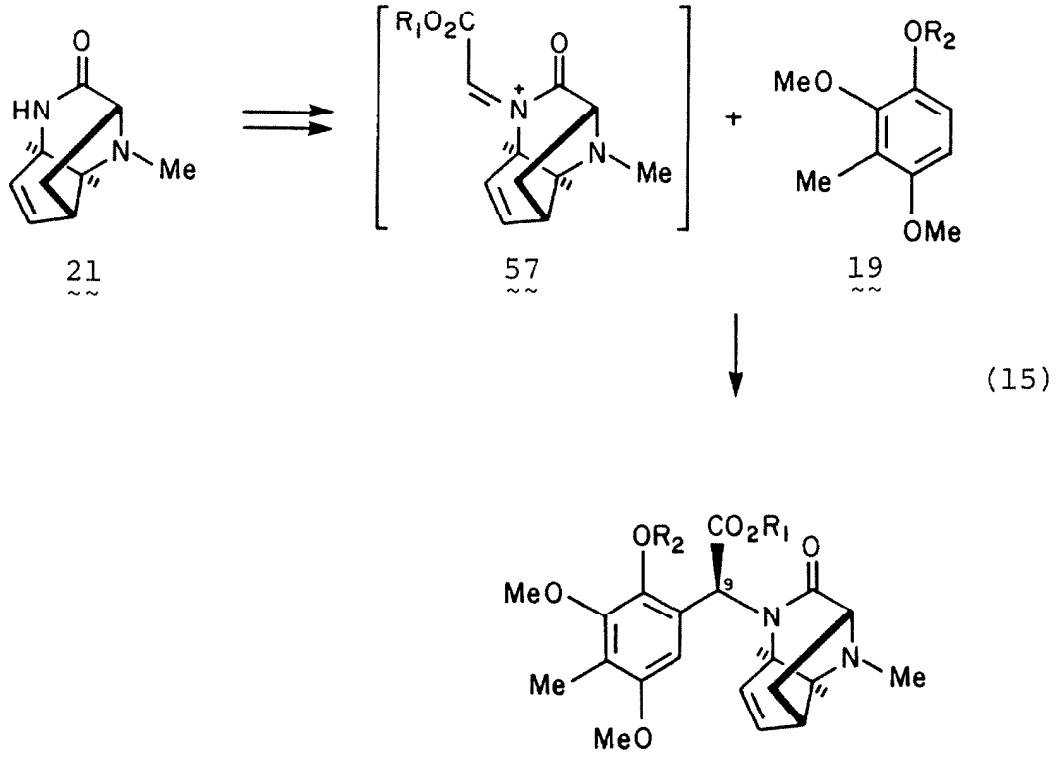
naphthyridinomycin A. Three of these four asymmetric centers were introduced with complete control of relative stereochemistry.



31 21

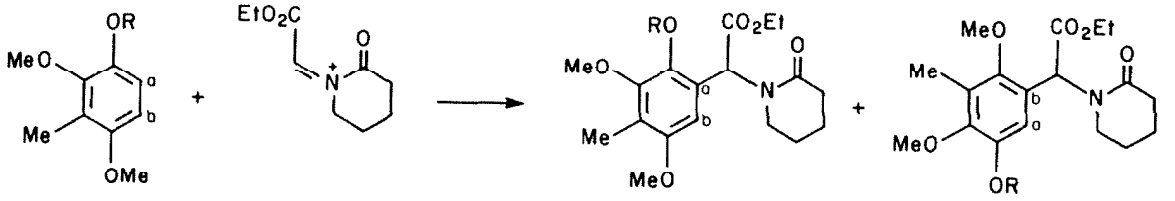
III. Model Studies on the Amidoalkylation Reaction

Introduction. Having developed a viable and efficient synthesis of tricyclic lactam 21, we next tackled the problem of attaching 21 to the aromatic nucleus as outlined in equation 15. The amidoalkylation reaction of (bis-acyl)immonium ion 57 with the functionalized benzene derivative 19, a reaction-type pioneered by Ben-Ishai,[15] appeared to be an attractive means of accomplishing this transformation. As noted previously, we desired to control both the regiochemical and stereo-

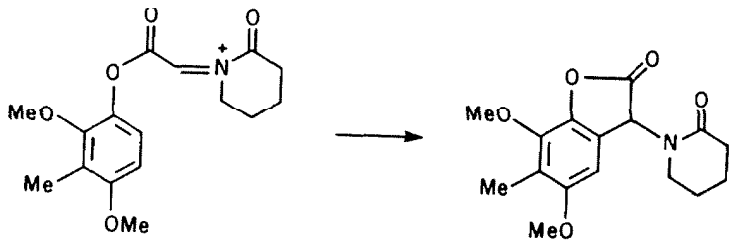


21 57 19 (15)

chemical outcome of this reaction. Due to the complexity of our system in comparison to those reported in the literature,[15] we felt it wise to explore this transformation in a simpler model system where valerolactam has been substituted for tricyclic lactam 21 (eqs 16 and 17). In doing this, we have eliminated the stereochemical issue, leaving only the regiochemical issue to be addressed.



19 58 59 60 (16)



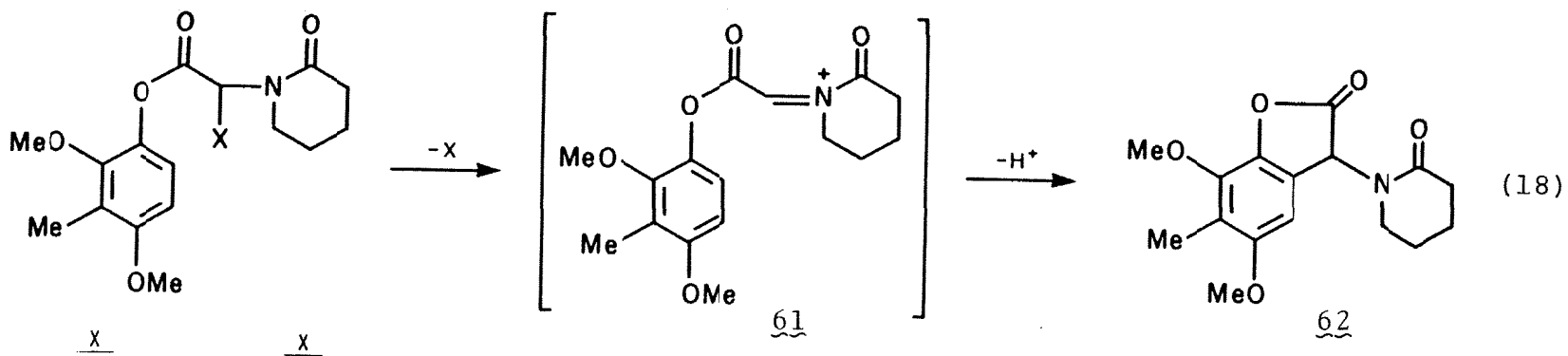
61 62 (17)

At the outset, we anticipated that little regioselectivity would be observed in the bimolecular alkylation (eq 16) because both positions a and b of aromatic ring 19 are highly activated for electrophilic substitution. However, one might expect to exercise some control over the site reactivity (formation of 59 in preference to 60) through the variation of R in 19 (R = H-, Me_3Si-, R'CO-, metal cation) and the conditions under which acylimmonium ion 58 is generated (nature of the counterion, presence of Lewis acids, etc.). Alternatively, a more certain solution to the regio-

chemical problem is the intramolecular amidoalkylation [12,15a,49] of acylimmonium ion 61 to afford benzofuran-2(3H)-one 62 (eq 17). Here, attachment of the acylimmonium ion to the aromatic nucleus via an ester linkage assures the desired regiochemical outcome. For this reason, the intramolecular approach was studied initially.

Results and Discussion. We proposed that the acylimmonium ion 61 could be generated by the selective ionization of an α-leaving group (X) from α-amido ester derivative 63 (eq 18). In light of the potentially sensitive nature of the intermediates en route to naphthyridinomycin A, it was desirable to find the mildest conditions under which this model intermediate (61) would form. The ability of "soft" metal cations[50] [Ag(I), Hg(II), Cu(I), Tl(III)] to promote the ionization of sulfides[51] and halides[52] in a mild and chemoselective manner led to the selection of sulfide 63a and choride 63b as model substrates. In addition, acetate 63c was selected on the basis of its projected ease of preparation and stability.

The synthesis of sulfide 63a from valerolactam (64) was accomplished in a 47% overall yield (four steps) as outlined in Scheme IX. The hydroxyl group of the



(18)

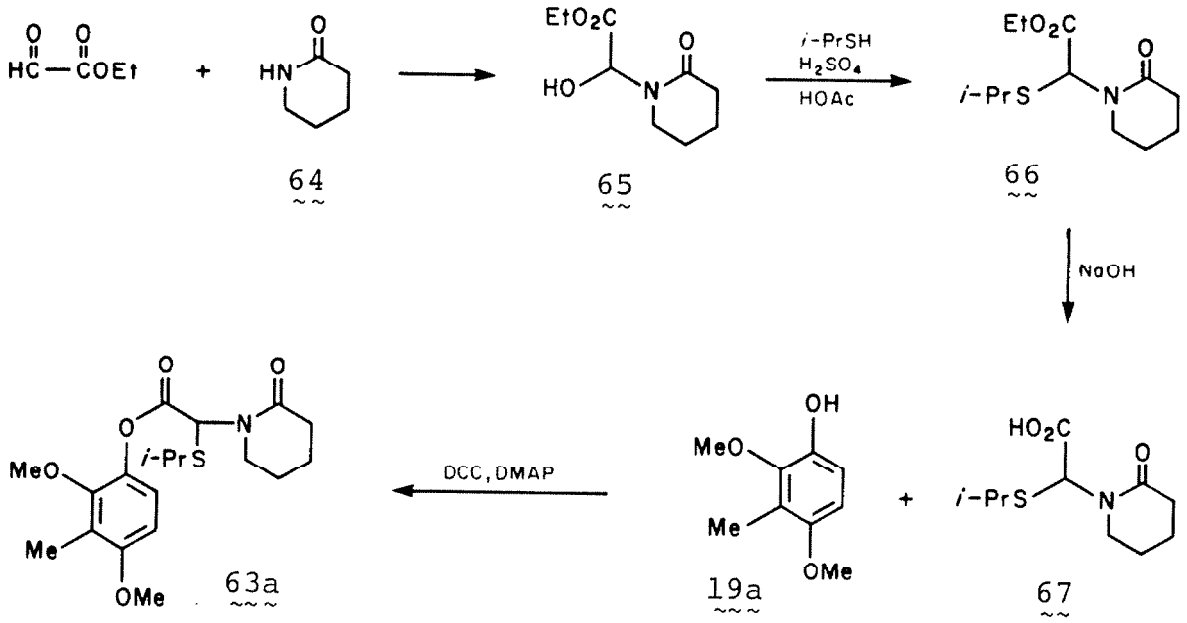
X	X
63a, S(i-Pr)	63e, OSO_2CH_3
b, Cl	f, $OCOCF_3$
c, OAc	g, $NHCOCH_3$
d, OH	h, $OSO_2C_7H_7$

Table 1. Intramolecular Amidoalkylation Reactions (eq 18).

Substrate	X	Lewis Acid	Conditions	Yield of 62
63a	S(i-Pr)	$CuOSO_2CF_3$	PhH, 75°C	60%
		$Hg(OSO_2CF_3)_2$	CH_2Cl_2, 25°C	80%
63b	Cl	$AgOSO_2CF_3$	CH_2Cl_2, 25°C	80%*
		$SnCl_4$	CH_2Cl_2, 25°C	66%*
63c	OAc	$BF_3 \cdot Et_2O$	PhH, 60°C	58%

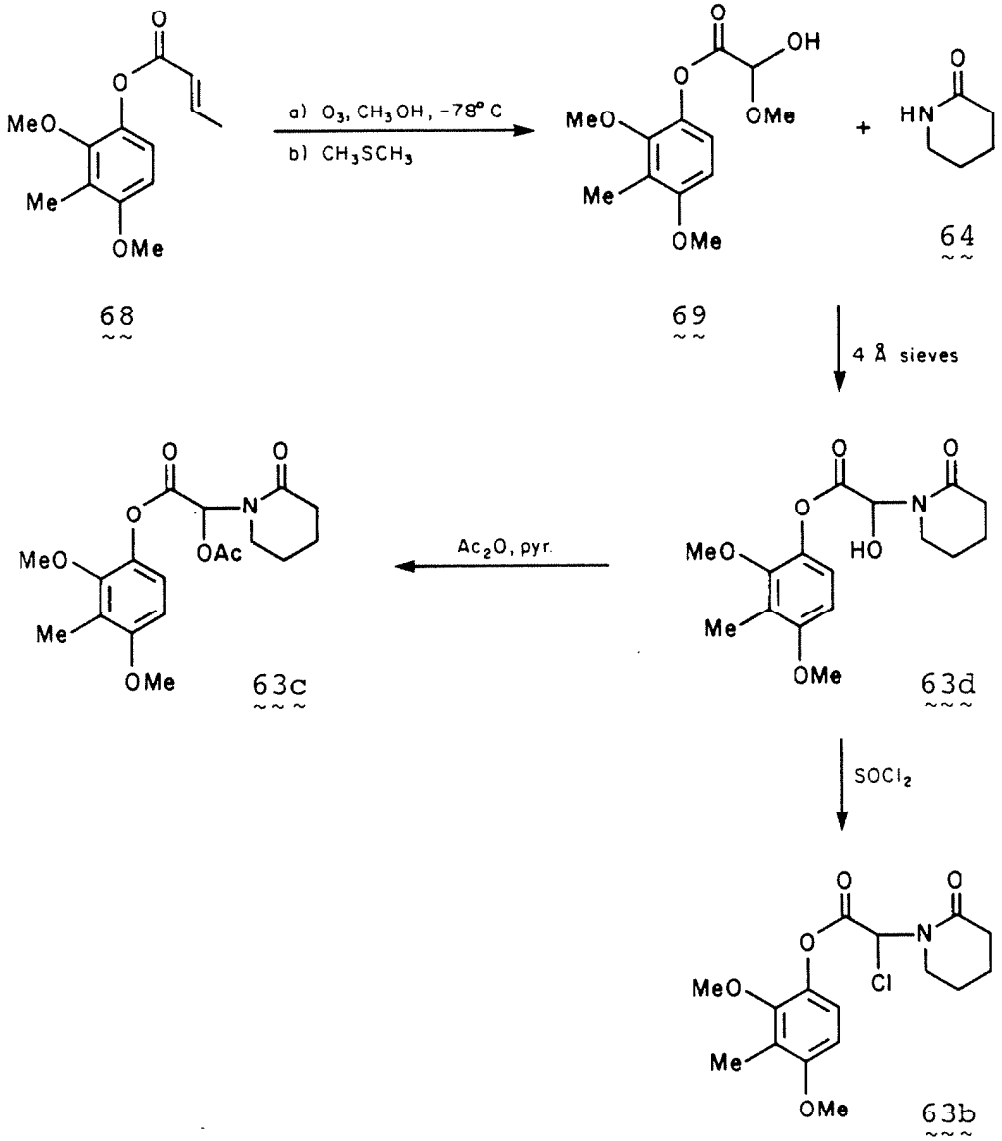
*Overall yield from 63d.

Scheme IX



valerolactam-ethyl glyoxalate adduct 65 was exchanged for the i-propylthio group, according to the procedure of Ben-Ishai,[53] to give the sulfide 66 (61% overall from 64). Saponification of the ethyl ester to afford carboxylic acid 67 (87%), followed by esterification[54] with phenol 19a (89%), readily provided the desired sulfide-ester 63a. The corresponding chloride (63b) and acetate (63c) were prepared according to Scheme X. Crotonate 68, readily prepared from phenol 19a and E-crotonic acid (91%),[54] was ozonized at -78°C in

Scheme X



68 69 64 63d 63c 63b

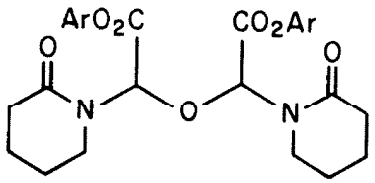
methanol followed by a dimethyl sulfide workup[55] to give phenyl glyoxalate-methanol adduct 69. Intermediate 69 was found to be somewhat unstable, decomposing gradually at room temperature to afford phenol 19a. Thus, 69 was generally used directly, without separation from the dimethyl sulfoxide co-product, in the subsequent reaction with valerolactam (64) to afford the glyoxalate adduct 63d (70-78%). Alcohol 63d could then be converted to chloride 63b and acetate 63c, employing standard procedures. Interestingly, an attempt to prepare mesylate 63e by treatment of 63d with methanesulfonyl chloride and triethylamine[37] at 0°C gave instead the chloride 63b as the major product.

The cyclization of i-propylsulfide 63a (eq 18) was initially examined employing copper(I) trifluoromethanesulfonate-benzene complex $[(CuOSO_2CF_3)_2 \cdot C_6H_6]$,[56] a reagent which has been shown to be a potent thiophile.[51f-k,56b] The reaction of 63a with excess copper(I) trifluoromethanesulfonate in benzene was slow at room temperature, but heating to 75°C gave the desired lactone 62 in 60% yield. The addition of hindered amine bases (ethyldiisopropylamine, 2,6-lutidine) in order to neutralize the trifluoromethanesulfonic acid which is generated, resulted in the isolation of

uncharacterized byproducts in addition to unreacted starting material (63a) and only a trace of lactone 62.

Mercury(II) reagents were found to be more reactive thiophiles for the formation of acylimmonium ion 61 from sulfide 63a (eq 18). The reaction of 63a with mercury(II) trifluoroacetate[57] in benzene at room temperature resulted in the rapid consumption of starting material and afforded alcohol 63d upon workup with aqueous sodium bicarbonate. It was presumed that the formation of alcohol 63d occurred via hydrolysis of the intermediate trifluoroacetate 63f during the workup procedure. Heating the reaction mixture to 80°C prior to the bicarbonate quench did not yield lactone 62. The above experiment suggested that a mercury(II) salt with a less nucleophilic counterion was required. Thus, mercury(II) trifluoromethanesulfonate[58] (70) was easily prepared via the reaction of mercury(II) oxide with trifluoromethanesulfonic anhydride. Mercury(II) trifluoromethanesulfonate was initially obtained as an acetonitrile solvate [$Hg(OSO_2CF_3)_2 \cdot (CH_3CN)_{1.74}$ by ^1H NMR]. The reaction of this solvate with sulfide 63a at room temperature gave, in addition to lactone 62 (41%), the Ritter product 63g (30%) (eq 18). However, the acetonitrile-free salt, obtained upon

drying the solvate at 110°C under vacuum, cleanly afforded lactone 62 in 80% yield upon reaction with sulfide 63c. In this and related amidoalkylation reactions, adventitious moisture has a deleterious effect, leading to the formation of dimeric byproducts of the structure 71 (mixture of two diastereomers).



Ar = 2,4-dimethoxy-3-methylphenyl

71

Although we have not yet initiated a general study on mercury(II) trifluoromethanesulfonate as a thiophilic agent, our initial observations indicate that it is considerably more potent than copper(I) trifluoromethanesulfonate in this capacity. Furthermore, mercury(II) trifluoromethanesulfonate possesses the additional advantages of being air stable and only moderately hydroscopic.

Conceivably, the cyclizations described above could have been promoted to a certain degree by the trifluoromethanesulfonic acid liberated during the

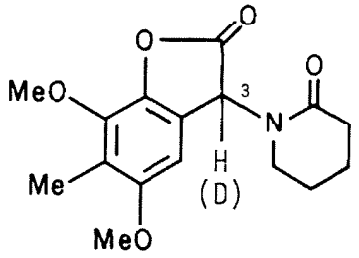
course of the reaction. With regard to this point, no reaction occurred upon treatment of sulfide 63a with one equivalent of trifluoromethanesulfonic acid in benzene at room temperature. Heating this reaction mixture to 80°C resulted in the partial conversion of 63a to phenol 19a, with only a trace of lactone 62 being formed as indicated by thin-layer chromatography.

The model lactone 62 could also be prepared by the treatment of chloride 63b with either silver(I) trifluoromethanesulfonate[59] or tin tetrachloride at room temperature (80% and 66%, respectively, from 63d) (eq 18). Interestingly, the reaction of chloride 63b with silver(I) p-toluenesulfonate[60] at room temperature gave a mixture of alcohol 63d and dimeric ethers 71 after an aqueous quench. However, heating this reaction mixture to 80°C prior to the aqueous quench resulted in the clean formation of lactone 62. This observation implicates the intermediacy of the covalent tosylate 63h, which is relatively stable towards ionization at room temperature. In contrast, apparently spontaneous cyclization occurs in the case of the trifluoromethanesulfonate counterion. This qualitatively establishes tosylate as the lower limit in leaving group ability for the facile generation of acylimmonium

ion 61. The following compilation of relative rates for departing groups in a typical S_N1 reaction helps to put these results into perspective; $CF_3SO_3^-$: $C_7H_7SO_3^-$: Cl^- = 2 x 10^{10} : 2 x 10^5 : 1.[61]

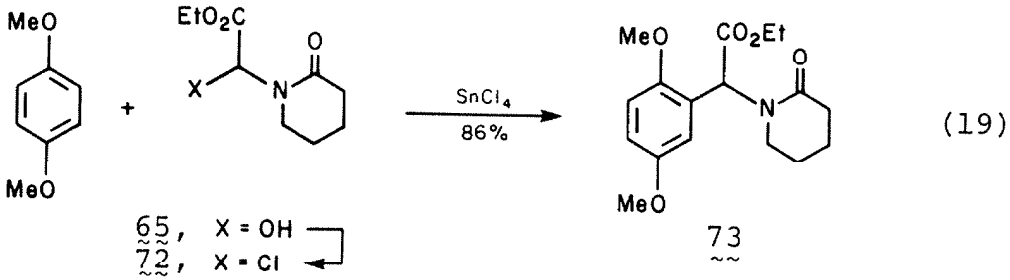
Finally, the reaction of acetate 63c with Lewis and protic acids afforded lactone 62 with varying degrees of success. In the most efficient procedure, heating acetate 63c and boron trifluoride etherate in benzene at 60°C gave lactone 62 in 58% yield (eq 18).

The spectral properties of the product isolated from these cyclization reactions are entirely consistent with the structure 62. Especially characteristic of the benzofuran-2(3H)-one ring system is the high carbonyl stretching frequency at 1812 cm^{-1}.[62] The acidic proton at the 3-position, which occurs as a broad resonance at δ 6.09 in the ^1H NMR, can be cleanly exchanged with deuterium simply by shaking a chloroform-d solution of 62 with sodium hydroxide-d in deuterium oxide for 15 min at room temperature.



62

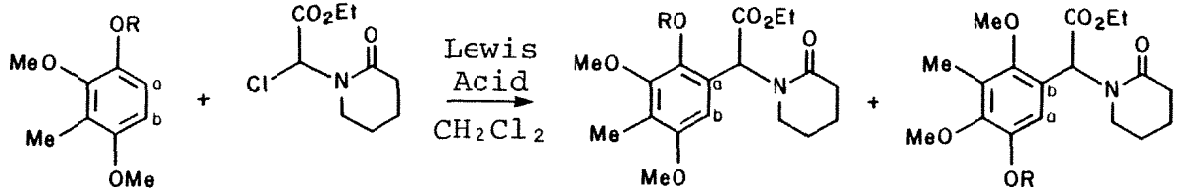
Due to the limited degree of success achieved upon application of the intramolecular amidoalkylation to intermediates en route to naphthyridinomycin A (see part IV of this report), we chose to explore the corresponding intermolecular approach. The viability of the intermolecular amidoalkylation was quickly demonstrated. Treatment of the valerolactam-glyoxalate adduct 65 with thionyl chloride gave the acylimmonium ion precursor, chloride 72 (99%). The reaction of chloride 72 with p-dimethoxybenzene and tin tetrachloride at room temperature afforded the arylated product 73 in 86% yield (eq 19). Subsequently, the more complex



(19)

reaction of chloride 72 with phenol derivatives 19a and 19b in the presence of Lewis acids was studied in some detail (eq 20). The results of this study are presented in Table 2.

Under all conditions examined (Table 2), a mixture



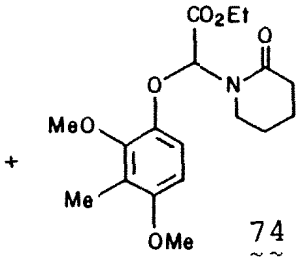
19a, R = H
b, R = $SiMe_3$

72

59a,b

60a,b

(20)



+ 74

Table 2. Lewis Acid Promoted Amidoalkylation Reactions of Phenol Derivatives 19a,b and Chloride 72 (eq 20).

Entry	Aromatic Substrate (equiv)	Lewis Acid (equiv)	Reaction Conditions	Ratio 59a:60a[a]	Isolated Yield (%) 59a+60a (74)[b]
A	19a (1.36)	$SnCl_4$ (1.42)	0°C, 1 h[c]	2.5	79
B	19a (1.19)	$SnCl_4$ (1.23)	-78°C, 1.5 h; 0°C, 0.5 h[d]	2.6	83
C	19a (1.13)	$BF_3 \cdot Et_2O$ (1.13)	0°C, 1 h; 25°C, 18 h	1.8	83

Table 2. Continued

Entry	Aromatic Substrate (equiv)	Lewis Acid (equiv)	Reaction Conditions	Ratio 59a:60a[a]	Isolated Yield (%) 59a+60a (74)[b]
D	19a (1.11)	$TiCl_4$ (1.25)	0°C, 1 h; 25°C, 18 h	0.17	25[e]
E	19a (1.26)	$AgOSO_2CF_3$ (1.23)	0°C, 1 h	2.7	29 (57)
F	19a (1.17)	$SnCl_4$ (2.21); $Et(i\text{-}Pr)_2N$ (1.12)	-78°C, 5 min; 0°C, 1 h[f]	7.5	37 (46)
G	19b (1.17)	$SnCl_4$ (1.30)	0°C, 1 h	0.76[g]	84
H	19b (1.25)	$SnCl_4$ (1.30)	0°C, 1 h[h]	0.78[g]	81
I	19b (1.12)	$SnCl_4$ (2.46)	0°C, 1 h[i]	2.0[g]	75
J	19b (1.21)	$AgOSO_2CF_3$ (1.67)	0°C, 1 h	0.23[g]	--[j]

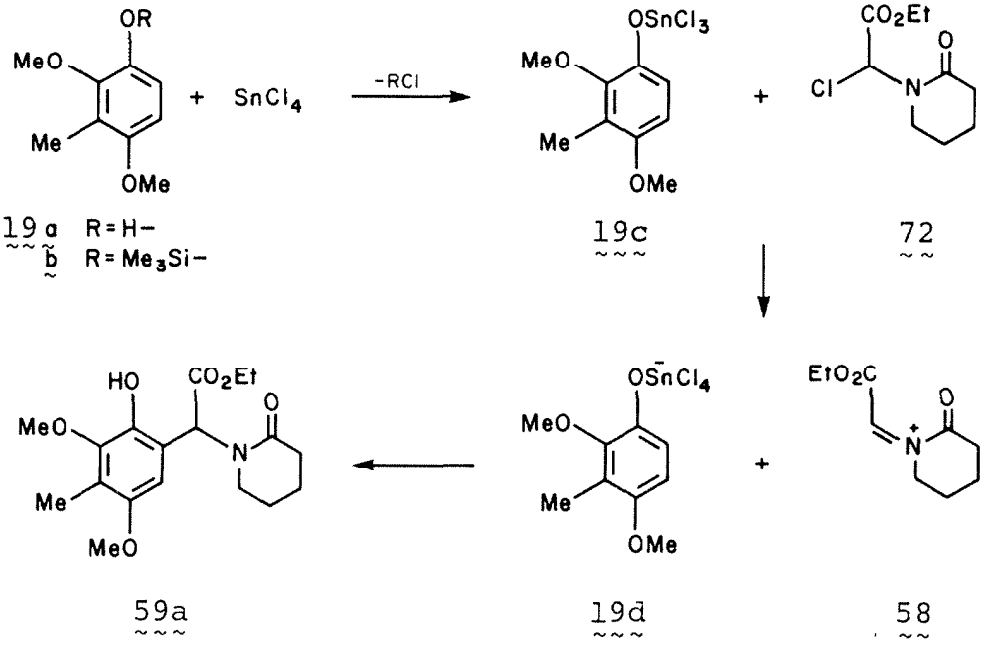
[a]Determined by ^1H NMR after chromatography. [b]Unless otherwise indicated, only small amounts of 74 (<10%) were noted in the crude products. [c]$SnCl_4$ and 19a were incubated for 1 h at 25°C before the addition of 72. [d]Reaction solution was warmed gradually from -78°C to 0°C over 1.5 h. [e]Much unreacted 72 was recovered. [f]$SnCl_4$, 19a and $Et(i\text{-}Pr)_2N$ were combined at -78°C prior to the addition of 72. [g]Ratios were determined after conversion of any silyl ether products into the corresponding phenols. [h]$SnCl_4$ and 19b were incubated for 2 h at 25°C before the addition of 72. [i]$SnCl_4$ and 19b were incubated for 6 h at 25°C before the addition of 72. [j]Not determined.

of regioisomers 59a and 60a was obtained, in ratios ranging from 7.5:1 to 0.17:1, respectively. Furthermore, small amounts (<10%) of the O-alkylated product 74 were typically formed, except in the cases of Entries E and F where 74 was the major product. The crude reaction mixtures derived from silyl ether 19b contained only minor amounts of silyl ether products (presumably 59b and/or 60b) in addition to the major products, phenols 59a and 60a. Thus, de-silylation has occurred to a significant extent at some point during the reaction. In the one experiment for which the silyl ether products were isolated by chromatography, only isomer 60b was obtained as evidenced by conversion to phenol 60a (CH_3OH, Et_3N). In general, the crude reaction mixtures derived from silyl ether 19b were treated with triethylamine in methanol to convert all silyl ethers into the corresponding phenols prior to determining the isomer distribution.

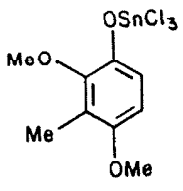
The regioselectivity observed in the intramolecular amidoalkylation reaction (Table 2) is not subject to any simple generalizations. However, there are certain points which warrant further discussion. It seems likely that silver(I) trifluoromethanesulfonate (Entries E and J) specifically assists in the ionization of the

chloride leaving group without interacting with the aromatic moiety. Thus, the regioisomer distribution observed with silver(I) trifluoromethanesulfonate is interpreted as being determined by the innate site reactivity of the unaltered aromatic nuclei 19a and 19b. On the other hand, with Lewis acids which are capable of coordinating to the oxygen substituents on the aromatic ring (e.g. $TiCl_4$, $BF_3 \cdot Et_2O$, $SnCl_4$) the situation becomes more complex. At the outset of our studies on the intermolecular amidoalkylation reaction, we hoped to

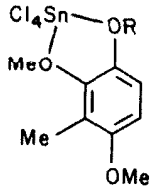
Scheme XI



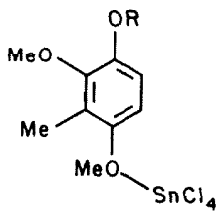
achieve high regioselectivity through the projected reaction sequence illustrated in Scheme XI. Exchange of the Lewis acid (illustrated for $SnCl_4$) for the R group of phenol derivative 19 would provide stannyl ether 19c, which could then assist in the ionization of chloride 72 to afford ion-pair 19d,58. Carbon-carbon formation within this ion pair was proposed to occur with high selectivity for the desired isomer, 59a. This scenario is complicated by the possibility of the direct reaction of such Lewis acid coordinated species as 19c, 75 and 76, as well as uncoordinated 19a,b, with acylimmonium ion 58.



19c



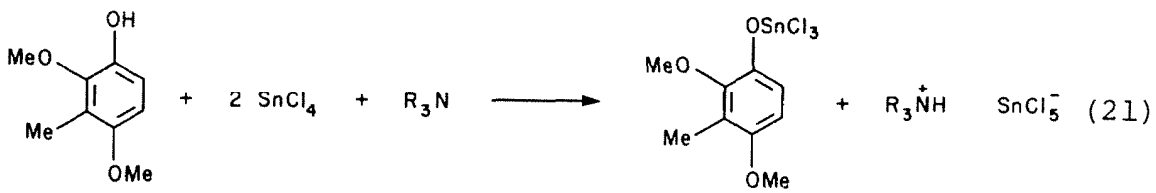
75



76

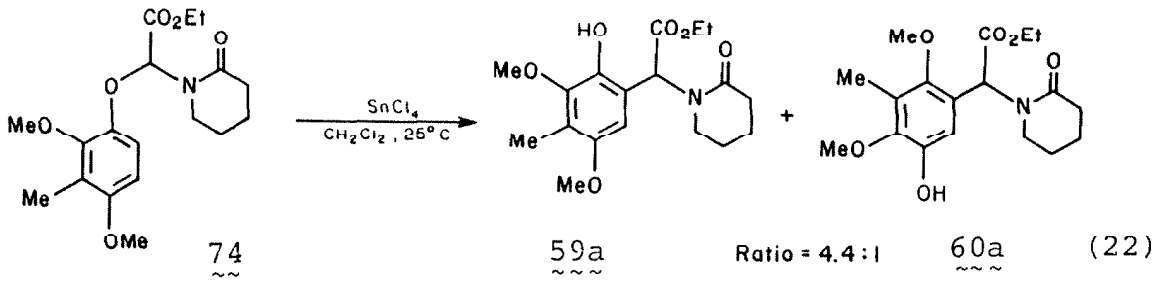
The results in Table 2 indicate that the sequence outlined in Scheme XI is not operating exclusively under the conditions examined. The reaction of phenol 19a and chloride 72 with tin tetrachloride (Entries A

and B) gave nearly the same isomer ratio (59a:60a ~ 2.6:1) as with silver(I) trifluoromethanesulfonate (Entry E). In contrast, the reaction of silyl ether 19b and chloride 72 is more selective for the desired regioisomer 59a with tin tetrachloride than with silver(I) trifluoromethanesulfonate. In the case of tin tetrachloride and 19b, the isomer ratio was found to be dependent on the exact reaction conditions (Entries G, H, I; optimum ratio of 59a:60a = 2.0:1). The highest regioselectivity among the C-alkylated products (59a:60a = 7.5:1) was achieved when the amidoalkylation of phenol 19a was performed in the presence of ethyldiisopropylamine (1.13 equiv) and tin tetrachloride (2.20 equiv) (Entry F). Perhaps, the removal of hydrochloric acid by the amine base promoted the formation of stannyl ether 19c (eq 21), which could then participate in the reaction sequence outlined in Scheme XI as described previously. Unfortunately, a high level of O-alkylation (46%) was observed in this reaction.



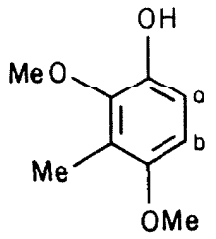
19a 19c

Potentially, the C-alkylated products 59a and 60a could have resulted from the kinetic formation and subsequent acid catalyzed rearrangement of aryl ether 74. In the case of the tin tetrachloride promoted reactions, the appropriate control experiment indicated the unlikelihood of the above proposal. Thus, the rearrangement of aryl ether 74 was found to be slow under conditions which rapidly led to the formation of C-alkylated products 59a and 60a from chloride 72 and phenol derivatives 19a,b ($SnCl_4$, 0°C). This rearrangement required over four hours at room temperature to go to completion, affording 59a and 60a in a 4.4:1 ratio (eq 22). Lactone 62 was formed in minor amounts in this reaction and was converted to 59a (EtOH, Et_3N) prior to isomer ratio determination.

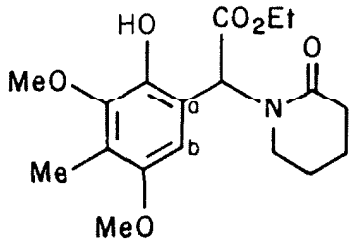


74 59a Ratio = 4.4:1 60a (22)

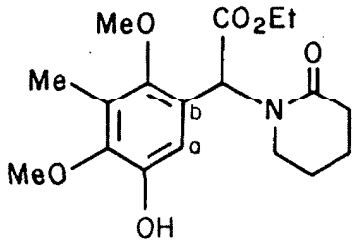
The structural assignments for regioisomers 59a and 60a were founded on firm chemical and spectral evidence. The preparation of an authentic sample of isomer 59a by opening lactone 62 with ethanol (EtOH, Et_3N, 25°C) allowed the unequivocable distinction between the two regioisomers obtained in the bimolecular amidoalkylation reaction. Furthermore, the chemical shifts and multiplicities of the aromatic signals in the ^{13}C NMR spectra of isomers 59a and 60a are consistent with predictions based upon the corresponding spectrum of phenol 19a (Table 3).[63]



19a



59a



60a

Table 3. ^{13}C NMR Spectral Data for Compounds 19a, 59a and 60a ($CDCl_3$).

Compound	Chemical Shift, ppm (Multiplicity) Carbon-a	Carbon-b
19a	112.1(d)	106.9(d)
59a	117.5(s)	107.9(d)
60a	114.2(d)	122.8(s) or 125.0(s)*

*A distinction between these two possible assignments could not be made.

Summary and Conclusions. The viability of both the intra- and intermolecular amidoalkylation reaction for the attachment of the aromatic nucleus to tricyclic lactam 21 was demonstrated in a model system. As anticipated, the intermolecular reaction afforded a mixture of regioisomers. The isomer distribution was found to be dependent on the aromatic substrate and the Lewis acid, as well as other factors. Alternatively, the intramolecular reaction provided a successful solution to the regiochemical problem.

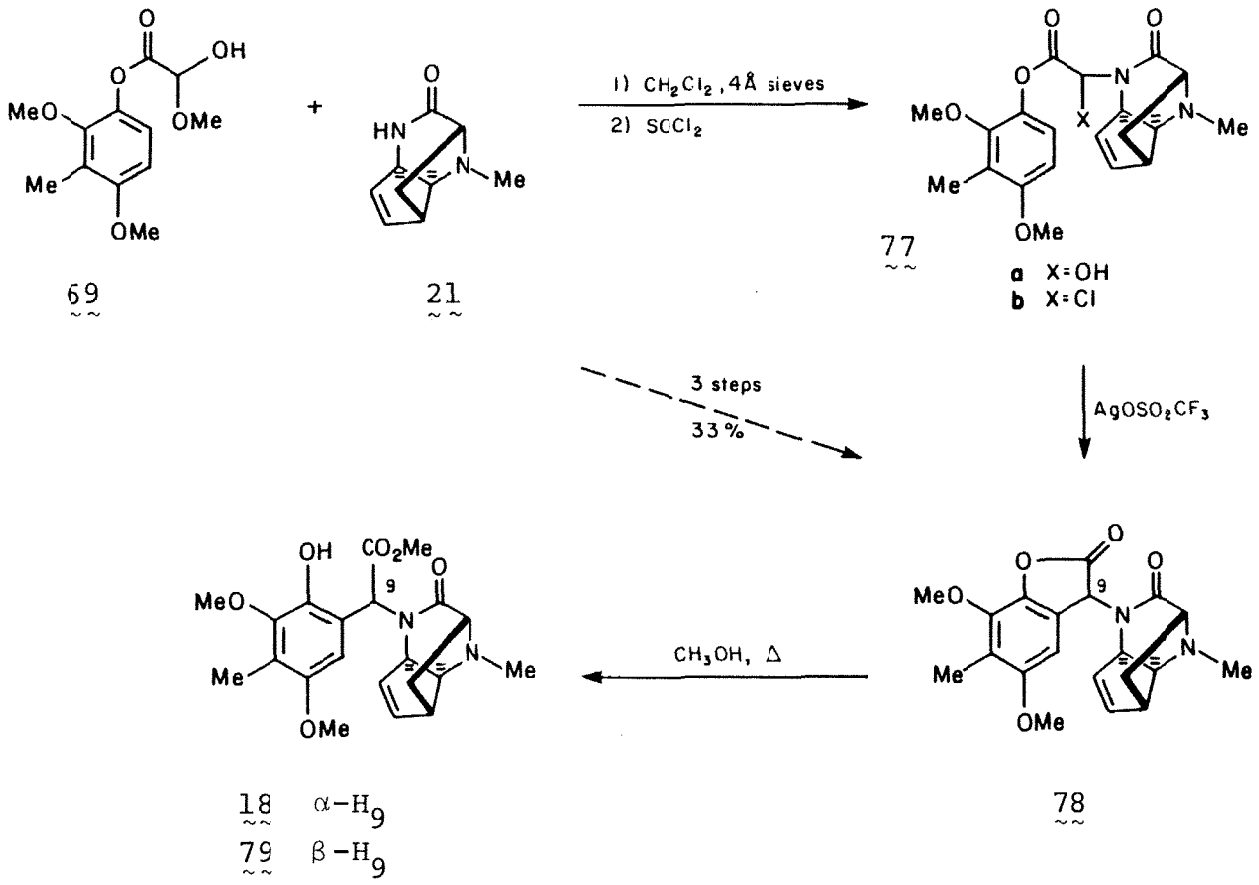
IV. The Construction of Pentacyclic Intermediate 93

Results and Discussion. Encouraged by our successful model studies on the amidoalkylation reaction, we next tackled the coupling of tricyclic lactam 21 to the aromatic nucleus (19) employing the methodologies which we had developed during the course of those earlier studies. We gleaned from the model chemistry that the intramolecular approach was required in order to control the regiochemical outcome of this reaction. Along these lines, lactam 21 was caused to react with glyoxalate-methanol adduct 69 to afford glyoxalate-lactam adduct

77a in 56% yield [2.2:1 mixture of isomers at C(9), naphthyridinomycin A numbering] (Scheme XII). Several aspects of this transformation deserve comment. In contrast to the corresponding model reaction, the crude glyoxalate-methanol adduct 69 was purified by flash chromatography[64] prior to reaction with lactam 21. This procedure was followed in order to remove the dimethyl sulfoxide coproduct which could not be readily separated from 77a after the subsequent step. Furthermore, excess 69 had to be employed due to its decomposition to phenol 19a, a side reaction which competes with the formation of 77a. Qualitatively, decomposition in this manner occurs more rapidly in the reaction of 69 with tricyclic lactam 21 than with valerolactam (64), suggesting that this side reaction may be catalyzed by the basic amine of 21. Adduct 77a was found to be somewhat unstable itself, decomposing gradually at room temperature and more rapidly upon (unnecessarily) prolonged exposure to silica gel during purification. These factors, in addition to the difficult chromatography required to separate adduct 77a from the excess 69 and phenol 19a, may be responsible for the only modest efficiency of this procedure.

Treatment of 77a with thionyl chloride gave the

Scheme XII



69 + 21 → 77 (a X=OH, b X=Cl)

77 → 78 → 18 (α-H_9) + 79 (β-H_9)

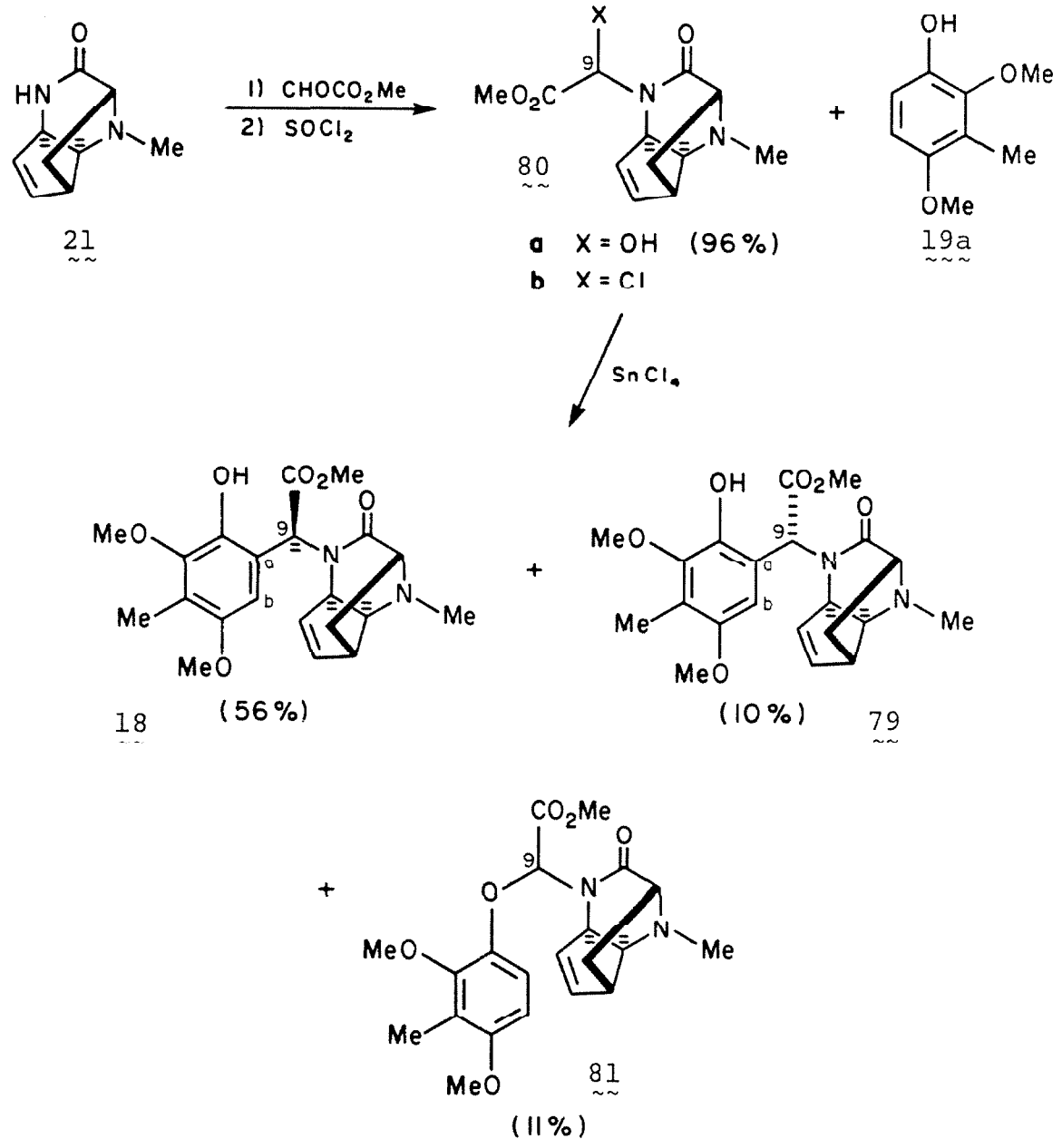
corresponding chloride 77b as its hydrochloride salt. It was anticipated that the basic amine of 77b would have to be protected as its salt for the subsequent amidoalkylation reaction, so that it would not intercept the intermediate acylimmonium ion. Thus, although the free amine (77b) could be isolated via neutralization of the salt with aqueous sodium carbonate, the hydrochloride was generally used directly in the next step.

The reaction of the hydrochloride of 77b with excess silver(I) trifluoromethanesulfonate[59] (CH_2Cl_2, 25°C) provided lactone 78 in 58% yield (overall from 77a) as a ~1.5:1 mixture of diastereomers at position 9. Similar to that observed for model lactone 62, the infrared spectrum of 78 possessed a carbonyl stretching vibration at 1810 cm^{-1} which is characteristic of the benzofuran-2(3H)-one ring system.[62] The formation of uncyclized by-products in this reaction, which most likely result from trapping the intermediate acylimmonium ion with water, could be minimized by the rigorous exclusion of adventitious moisture. The reactive lactone ring of 78 could be cleaved by heating a methanol solution of this substance to reflux, affording a 1:1 mixture of isomeric esters 18 and 79.

Considering the unsatisfactory overall yield of lactone 78 obtained via the intramolecular amidoalkylation sequence, we decided to investigate the intermolecular approach. Our model studies suggested that the regioselectivity of the reaction with respect to the aromatic ring would be lower than desired; however, we hoped that a higher overall yield would more than compensate for this disadvantage. The results of this study are outlined in Scheme XIII.

The reaction of methyl glyoxalate with lactam 21 afforded the adduct 80a in 96% yield [2:1 mixture of diastereomers at C(9)]. This transformation was accomplished employing "free" (ie. non-polymerized and non-hydrated) methyl glyoxalate,[65] which was obtained by redistilling once-distilled material from phosphorous pentoxide and collecting the distillate at -78°C. In this manner, samples containing up to 95% "free" glyoxalate (estimated by ^{1}H NMR) could be obtained. Treatment of glyoxalate adduct 80a with thionyl chloride followed by neutralization with aqueous sodium carbonate gave chloride 80b [1:1 mixture of diastereomers at C(9)] as the free base in near quantitative yield. In the crucial step, the reaction of chloride 80b with tin tetrachloride (2.6 equiv) and phenol 19a (1.3 equiv) resulted in a mixture

Scheme XIII



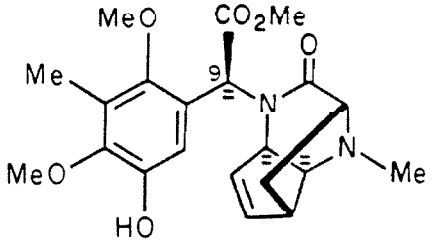
21 80 a X = OH (96%) 19a

b X = Cl

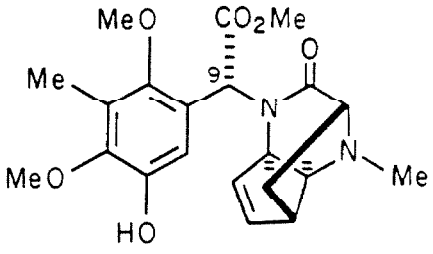
18 79 81

of alkylated products (CH_2Cl_2, 25°C, 40 h). The separation of this mixture was accomplished with difficulty by medium pressure liquid chromatography, affording C-alkylated products 18 and 79 in 56% and 10% yields, respectively, and O-alkylated product 81 [3:1 mixture of diastereomers at C(9)] in 11% yield (overall from glyoxalate adduct 80a). In addition, a 5% yield of the methoxy compound 80c (X = OCH_3) was isolated [1.2:1 mixture of diastereomers at C(9)], resulting from the reaction of recovered chloride 80b with the methanol in the column eluent. More conveniently, pure desired isomer 18 was obtained in a 48% yield (overall from 21) by direct crystallization from the crude reaction mixture upon the addition of ether.

Without the appropriate authentic samples, we could not accurately determine the extent to which the undesired regioisomers 82 and 83 were formed in this



82



83

reaction, if at all. However, since 82 and 83 have escaped detection, we estimate that they comprise less than 5% of the crude product. Thus, the intermolecular amidoalkylation reaction has occurred with a level of regio- and stereoselectivity that was not anticipated.

The regiochemical assignments indicated in structures 18 and 79 for the intermolecular amidoalkylation products were initially based upon their ^{13}C NMR spectra. The chemical shifts for aromatic carbons a and b (Scheme XIII) of 18 occur at 117.0 ppm and 107.7 ppm, respectively, and those of 79 occur at 117.3 ppm and 107.8 ppm, respectively. Upon comparison with the ^{13}C NMR spectra of model compounds 59a and 60a (refer to Table 3), these spectral data strongly suggest that both isomers 18 and 79 possess the desired regiochemistry. In addition, the following chemical correlations further support the structural relationship between 18, 79 and lactone 78: (1) Each of the intermolecular amidoalkylation products (18 and 79) were identical to one of the two isomeric methyl esters which formed upon the cleavage of lactone 78 with methanol. (2) Heating a chloroform-d solution of major isomer 18 and triethylamine to reflux in a Soxhlet apparatus charged with 4Å sieves resulted in the slow formation

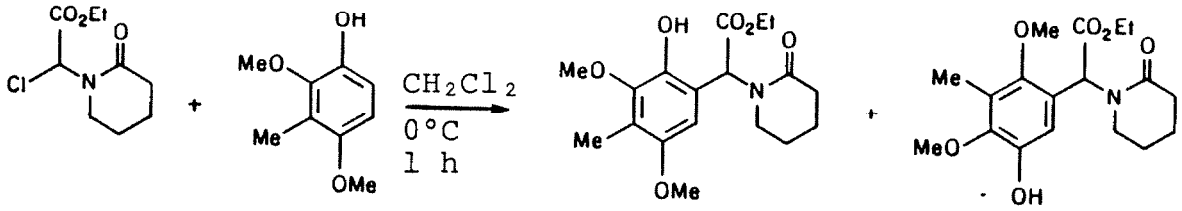
of lactone 78 as a mixture of isomers at position 9, without significant equilibration of 18 to 79. (It is assumed that the mixture at position 9 obtained in the lactone product was generated after lactonization had occurred). (3) Treatment of 18 with sodium methoxide in methanol at 0°C rapidly established a 1.6:1 ratio of 79:18, in addition to a trace of lactone 78. This is considered to be the equilibrium mixture.

The assignment of the desired stereochemistry at position 9 indicated in structure 18 to the major product of the intermolecular reaction was based upon spectral and X-ray studies on later intermediates (vide infra).

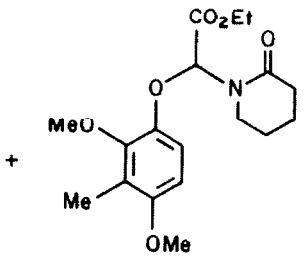
As noted above, the relatively high degree of regio- and stereoselectivity observed in the intermolecular amidoalkylation reaction was unexpected. Although an explanation for the selectivity is not readily apparent, several aspects of this transformation warrant brief discussion.

With regard to the regiochemical issue, the results of two highly relevant model experiments are reproduced in equation 23. In contrast to the corresponding reaction of chloride 80b, the tin tetrachloride promoted reaction of model chloride 72 with phenol 19a was only

slightly regioselective (reaction A, eq 23). The presence of the basic nitrogen in chloride 80b appeared to be the only obvious structural difference between chlorides 72 and 80b that could have caused this difference in selectivity. Thus, the amidoalkylation reaction of 72 was performed in the presence of ethyldiisopropylamine (reaction B, eq 23) in order to more closely mimic the reaction of 80b. Indeed, this pro-



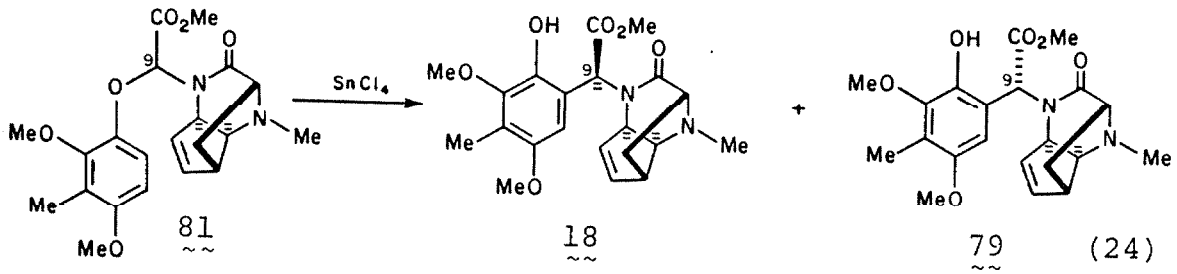
72 19a 59a 60a



74 (23)

Reaction	Conditions	59a:60a	Yield (%) 59a+60a	74
A	$SnCl_4$ (1.4 equiv)	2.5:1	79	<10
B	$SnCl_4$ (2.2 equiv), $Et(i\text{-}Pr)_2N$ (1.1 equiv)	7.5:1	37	46

cedure resulted in enhanced regioselectivity (59a:60a = 7.5:1) and a possible explanation for this effect has been discussed above (see part III of this report). However, the major product of this model experiment was aryl ether 74, the result of O-alkylation. It therefore became of interest to probe the stereochemical outcome of the rearrangement of aryl ether 81. Treatment of aryl ether 81 with excess tin tetrachloride (CH_2Cl_2, 25°C) resulted in partial conversion to the corresponding C-alkylated products (eq 24). Chromatographic separation of the crude product gave a 86:14 mixture of 18:79 (29% combined yield) in addition to recovered 81 (40%).[83] No evidence for the formation of regioisomers 82 and 83 was observed. The isomer distribution obtained in this experiment is very similar to that obtained in the tin tetrachloride promoted reaction of chloride 80b and phenol 19a (18:79 = 85:15). Thus, it is possible that aryl ether 81 is an intermediate in the amidoalkylation reaction outlined in Scheme XIII.



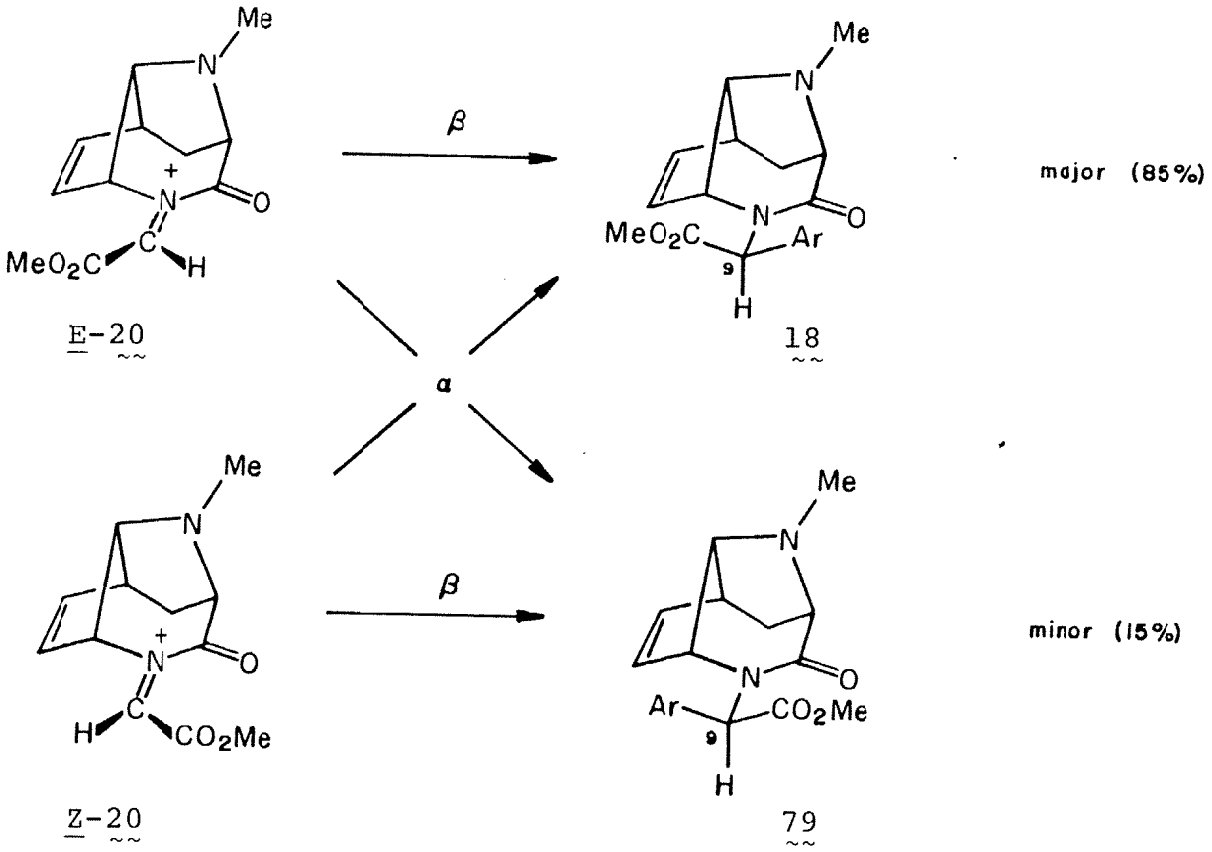
81 18 79 (24)

Ratio = 86:14

Concerning the stereochemical outcome of the intermolecular amidoalkylation reaction at position 9, two independent issues must be considered (Scheme XIV): the stereochemistry of the acylimmonium ion intermediate (E-20 versus Z-20) and the diastereoface selectivity for attack of the aromatic ring on the acylimmonium ion (α- versus β-attack). According to this analysis, the major isomer 18 results from β-attack on E-20, α-attack on Z-20, or a combination of both of these modes. There are two factors which may significantly effect the outcome of these two independent stereochemical issues: (1) Chelation of the Lewis acid between the ester and the amide carbonyl groups of acylimmonium ion precursor 80b, as illustrated in structure 84, would encourage the formation of Z-20. (2) The state of the basic nitrogen of 20 may strongly influence the diastereoface selectivity of nucleophilic additions to this electrophile. The amino group of 20 is presumed to exist in quaternary form under the reaction conditions, being either protonated (bearing an $SnCl_5^-$ counterion) or coordinated directly to tin tetrachloride. In effect, this serves to add another chiral center to the intermediate. If the stereochemistry at the tetrahedral nitrogen is as illustrated

Scheme XIV

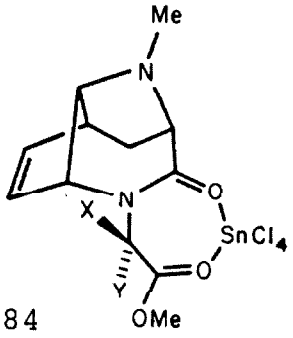
C-9 Stereoselection



E-20 18

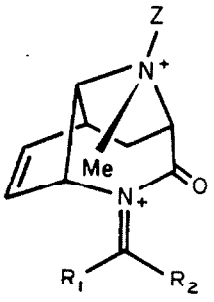
Z-20 79

in structure 85, molecular models suggest that the N-methyl group should deter β-attack. In the case of the alternative stereochemical possibility illustrated in structure 86, the extent of steric shielding of β-attack will depend on the effective size of the Z group, a factor which is difficult to estimate. In conclusion, firm predictions as to the favored geometry of 20 or the facial bias for nucleophilic addition to this acylimmonium ion cannot be made without additional experimental data. However, if the two effects discussed above are operating, the favored reaction course should involve α-attack on Z-20, leading to the observed major product, 18.

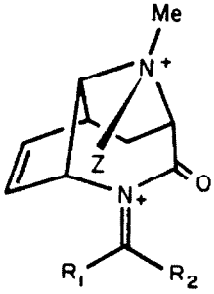


84

X, Y = H, Cl



85

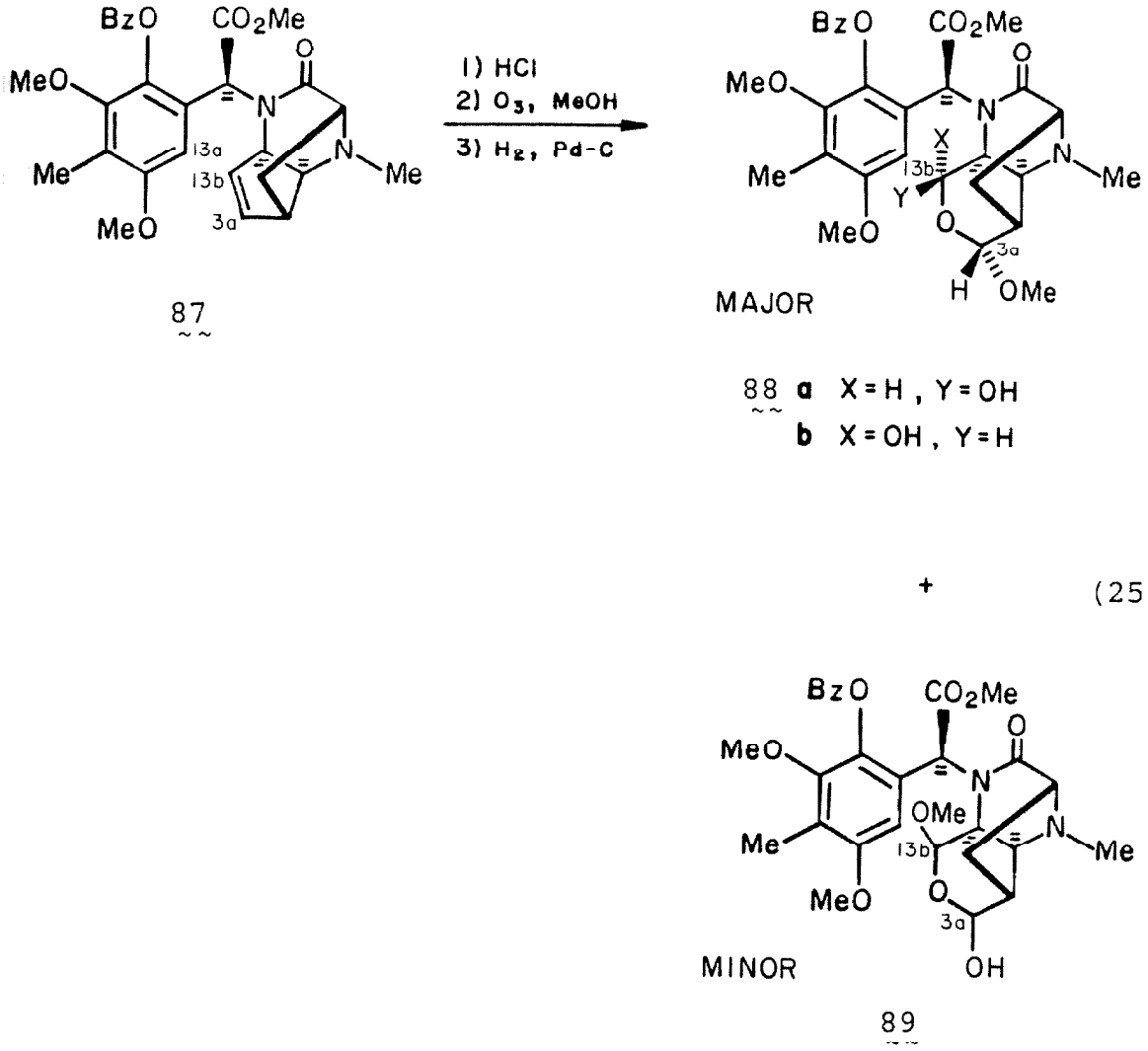


86

R_1, R_2 = H, CO_2Me

Z = $SnCl_4^-$ or H, $SnCl_5^-$

Having coupled the aromatic nucleus and tricyclic lactam 21 in a stereoselective manner, our attention turned to the construction of the 13a-13b carbon-carbon bond (naphthyridinomycin A numbering). This transformation would involve two stages: oxidative cleavage of the 3a-13b double bond of 18 (eq 25) to afford the aforementioned dialdehyde equivalent, and then bond formation between positions 13a and 13b via a Friedel-Crafts cyclization. Before proceeding in this direction, phenol 18 was protected as its benzoate ester (87) employing standard conditions (PhCOCl, pyridine, 98%). The hydrochloride salt of 87 was ozonized in methanol at -78°C employing Sudan III as an indicator,[66] followed by reductive cleavage of the peroxide intermediates (H_2, 5% Pd-C).[67] As anticipated, this procedure did not afford a dialdehyde. Instead, the product was a mixture of regioisomeric cyclic hemiacetals 88 and 89. This consequence was highly desirable, in that the stable nature of the tetrahydropyran ring serves to protect the latent dialdehyde from potentially destructive side reactions in the subsequent steps (ie. isomerization at the α-centers, β-elimination, retro-Mannich fragmentation, aldol condensation) while still permitting the Friedel-Crafts cyclization to



87

88 **a** X = H, Y = OH
b X = OH, Y = H

\+ (25)

89

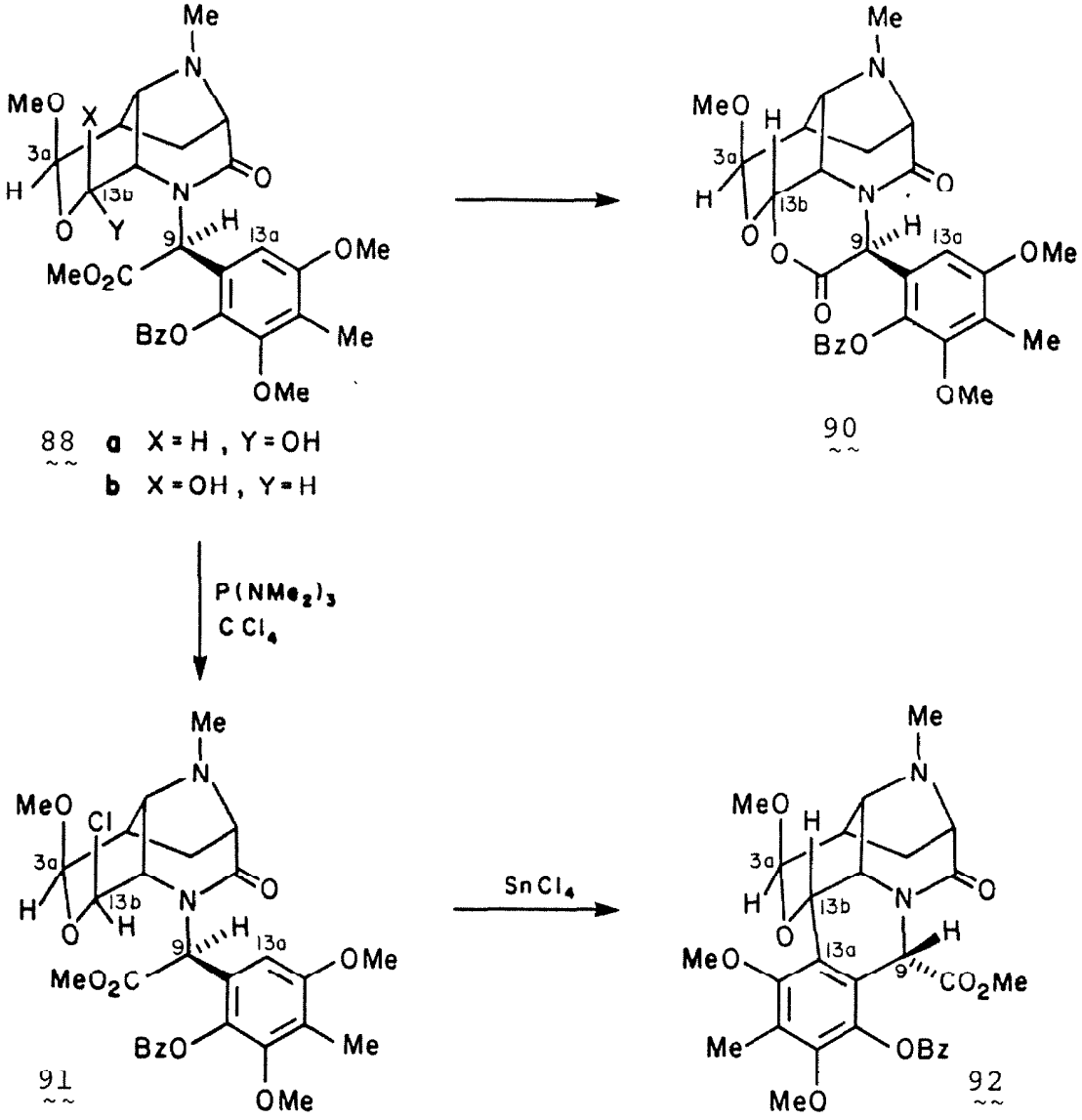
occur via an oxonium ion[68] at position 13b (vide infra).

The major component of this mixture of tetrahydropyranols (as judged by ^{1}H NMR and TLC) could be isolated in up to 70% yield by chromatography and was shown to be a mixture of 88a and 88b (88b:88a ~ 1.3:1 by ^{1}H NMR).[69] The regiochemical assignment indicated

for 88a,b was based upon subsequent chemical transformations, and the stereochemical assignment indicated at position 3a (axial OMe) was based upon spectral and X-ray studies on later intermediates. In addition to 88a,b, lesser amounts (~18%) of the regioisomeric tetrahydropyranol 89 were isolated as a mixture of two stereoisomers (^{1}H NMR). The regiochemical assignment indicated in structure 89 was based upon the occurrence of the anomeric (13b) methoxyl groups at an anomalously high field position in the ^{1}H NMR spectrum of this mixture (δ 2.98, isomer A; δ 3.01, isomer B). This phenomenon is most readily explained by through-space shielding of these methoxyl groups by the neighboring aromatic ring.[72] Further characterization of 89 was hampered by the relatively small amounts in which it was isolated.

In an attempt to effect the direct Friedel-Crafts cyclo-dehydration of pyranols 88a,b to the pentacycle 92, this isomeric mixture was treated with excess tin tetrachloride in dichloromethane at room temperature (Scheme XV). Under these reaction conditions, partial conversion to a new product occurred, which was separated from unreacted 88a,b by medium pressure liquid chromatography. The spectral data obtained for this

Scheme XV


Me
N
MeO
X
3a
H
O
13b
Y
O
9
H
13a
OMe
MeO2C
BzO
Me
OMe
88 a X=H, Y=OH
b X=OH, Y=H
90
P(NMe2)3
CCl4
Cl
91
SnCl4
CO2Me
OBz
92

substance indicated that it was lactone 90, not the desired 92. We assumed that lactone 90 had formed via the intramolecular acylation of the 13b-hydroxy group of 88a by the 9-methoxycarbonyl group. Indeed, slow lactonization to form 90 with the concomitant release of methanol resulted when a sample of 88a,b was allowed to stand in chloroform-d solution at room temperature in the absence of added catalysts.

The structure proof for lactone 90 rests on firm spectral evidence. Specifically, the presence of a singlet at δ 6.93 in the ^{1}H NMR spectra and a resonance at 108.5 ppm in the ^{13}C NMR spectra clearly demonstrated that the aromatic ring still possessed an unsubstituted carbon [C(13a)], thereby disqualifying structure 92. In addition, the resonances at 101.7 ppm and 91.4 ppm observed in the ^{13}C NMR spectra of 90 are consistent with the two acetal-type carbons at positions 3a and 13b, respectively.[73,74] The assignment of the stereochemistry at position 13b indicated in structure 90 follows the conclusion that the alternative stereochemistry would require the tetrahydropyran ring to exist in the highly strained boat conformation.

In light of these results, it was concluded that the conversion of the 13b-hydroxyl group of 88a,b to a

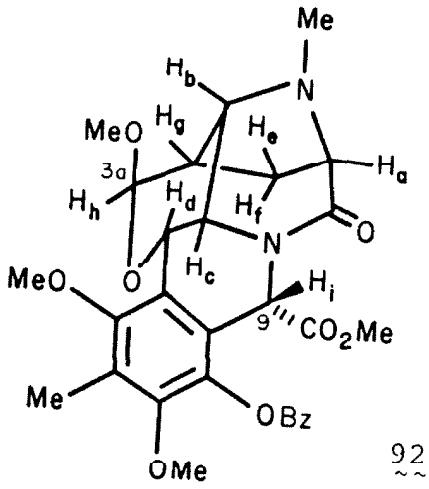
more reactive leaving group was required to both facilitate the desired Friedel-Crafts cyclization and eliminate lactonization as a side reaction. Following this logic, tetrahydropyranols 88a,b were treated with hexamethylphosphorous triamide and carbon tetrachloride[75] (CH_2Cl_2, -78°C to 25°C) to afford a mixture of pyranosyl chloride 91 and hexamethylphosphoric triamide (Scheme XV). The ^1H NMR spectrum of this mixture revealed that the chloride was predominantly ($\geq$90%) a single isomer. This observation is consistent with hypothesis that 88a and 88b are isomeric at position 13b. The axial stereochemistry depicted in structure 91 was assigned on the basis of the large anomeric effect (~2.7 kcal/mol) which is characteristic of pyranosyl chlorides.[76,77]

The crude chloride 91 was not purified, but was treated directly with excess tin tetrachloride in dichloromethane (-78°C to 0°C) to effect the Friedel-Crafts cyclization (Scheme XV). This procedure afforded the desired pentacycle 92 as the major product, presumably via an intermediate oxonium ion at position 13b. It was assumed that the stereochemistry at the newly formed center (13b) is as depicted in structure 92 because the transition state leading to the alternate stereochemistry is highly strained. In order to avoid

the material losses generally incurred during the chromatographic purification of tetrahydropyranols 88a,b, the entire reaction sequence from olefin 87 was performed without purification at the intermediate stages to afford pentacycle 92 in 42% overall yield (three steps).

Most of the spectral data accumulated for the product of this Friedel-Crafts cyclization were consistent with the proposed structure 92. Accordingly, the ^{1}H NMR spectrum no longer contained an aromatic proton resonance. The ^{13}C NMR spectrum contained only one acetal-type carbon resonance (101.2 ppm), and the signal for the aromatic carbon (13a) which underwent substitution was shifted considerably downfield (15-20 ppm). There was, however, one singularly disturbing aspect of the ^{1}H NMR spectra of 92 recorded at 34°C in chloroform-d; that is, only three sharp methoxyl signals of comparable intensity were evident, even though the integration of the methoxyl containing region (δ 3.2-4.0) was consistent with the presence of the required four methoxyl groups. Furthermore, the proton α- to the methoxycarbonyl group (H_1) appeared as an unusually broad signal. By means of a variable-temperature ^{1}H NMR study, we were able to

demonstrate that these unusual spectral properties were the result of some time-dependent phenomenon.[78] The highlights of this experiment are illustrated in Figure 6 for the δ 3.0-6.0 region. At +60°C in toluene-$\underline{d}_8$, four sharp methoxyl signals (labeled A, B, C, D) and three reasonably sharp methine signals (H_d, H_h and H_i)



92

were observed in the 90 MHz ^{1}H NMR spectra of 92 (Figure 6-a). Upon cooling to +25°C, methoxyl A and methines H_d, H_h and H_i broadened considerably (Figure 6-b). Further cooling to -20°C caused the separation of methoxyl A and methines H_d, H_h and H_i into two resonances each, indicating that the sample temperature was below the coalescence point of these signals (Figure 6-c).

We propose that this temperature-dependent effect is a result of hindered rotation about one or more of

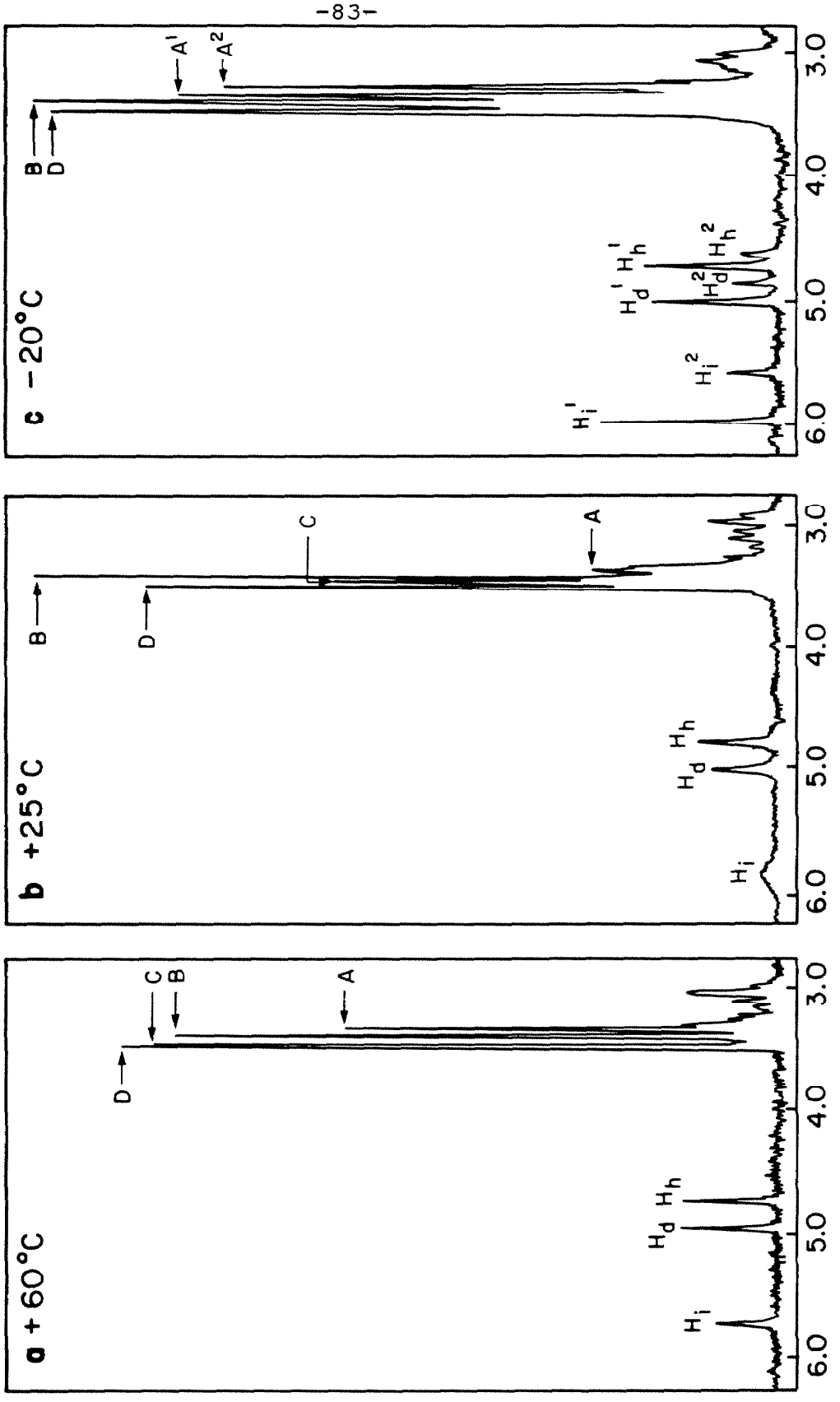
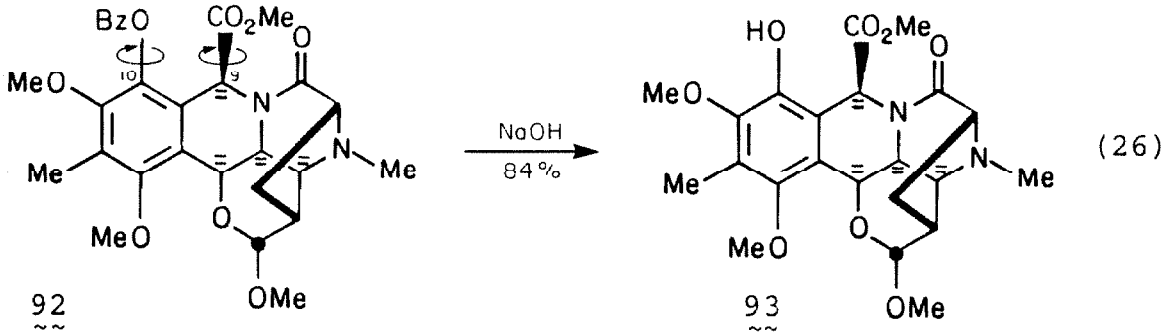


Figure 6. Variable-Temperature ^1H NMR Study of 92 (90 MHz, toluene-d_8).

the single bonds of 92,[78] and suggest that the benzoate ester may be intimately involved. Selective hydrolysis of the benzoate group of 92 was effected without disturbing the 9-methoxycarbonyl group, affording the corresponding phenol, 93, in 84% yield (NaOH, H_2O, CH_3OH, THF, 25°C) (eq 26). The ^1H NMR spectrum of phenol 93 recorded at 34°C in chloroform-d did not exhibit the broadened resonances which are characteristic of benzoate 92. Upon examination of molecular models, we concluded that hindered rotation is possible about

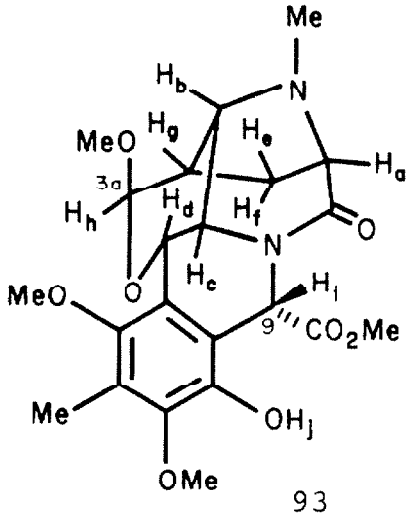


92 93 (26)

both the C(10)-O and C(9)-CO_2Me bonds of 92. The benzoate group is directly involved in the former rotation, and serves as a steric barrier with respect to the latter rotation.

In order to determine the relative stereochemistry at the 9- and 3a-positions, a nuclear Overhauser enhancement[79,80] study of phenol 93 was performed

using the NOE difference technique[80] at 500 MHz. The results of this study are collected in Table 4. The 500 MHz ^{1}H NMR spectrum of 93 was assigned via analysis of chemical shift data and coupling patterns



93

Table 4. Nuclear Overhauser Enhancement Study of Phenol 93[a] (500 MHz).

Proton Irradiated	Proton Enhanced
H_i	H_c, H_j
H_c (3a-OMe)[b]	H_i, H_d, NMe, (H_h)[b]
H_h	H_f, H_g, 3a-OMe

[a] $CDCl_3$ solution. [b] Partial irradiation of 3a-OMe could not be avoided in this experiment, and is most likely directly responsible for the enhancement of H_h.

(see Table 9 for detailed spectral data). Irradiation of H_i resulted in an enhanced signal for H_c, and vice versa. This observation strongly suggests that H_i and H_c have a syn relationship as depicted in structure 93 and prior intermediates, which corresponds to the desired configuration at position 9. Irradiation of H_h resulted in an enhanced signal for H_f, strongly suggesting that H_h and H_f have a syn relationship as depicted in structure 93 and prior intermediates.

Although our spectral evidence was quite convincing, we desired unequivocable proof of the overall structure and stereochemistry of these advanced intermediates. For this reason, a single crystal X-ray diffraction study of benzoate 92 was performed. Suitable crystals were obtained by the vapor diffusion of ether into a solution of 92 in benzene. The results of the X-ray study, carried out by N. S. Mandel and G. S. Mandel at the Medical College of Wisconsin,[36] are presented in Figure 7. The crystal structure of 92 is identical to the structure deduced on the basis of spectral and chemical evidence.

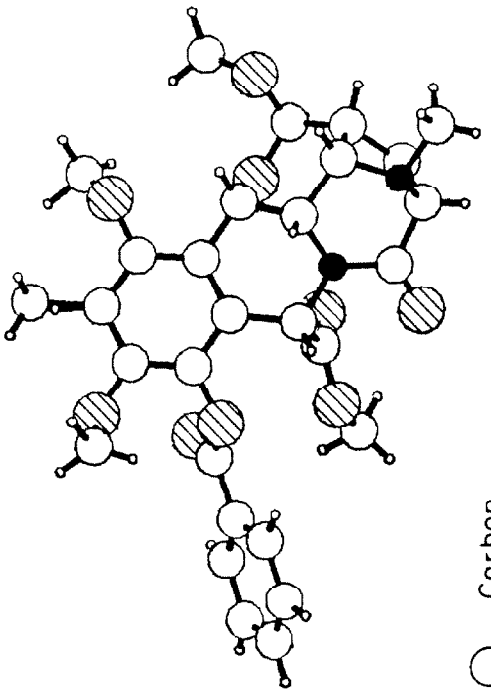


Figure 7. X-Ray Crystal Structure of 92.

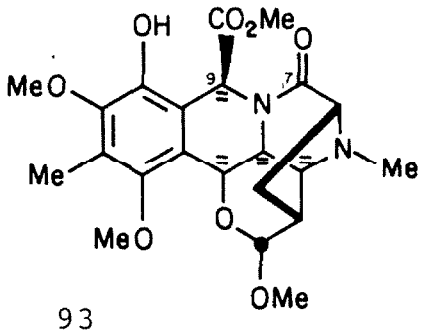
Summary and Conclusions. The research described in this report has culminated in the preparation of phenol 93, an advanced intermediate en route to naphthyridinomycin A. Phenol 93 has been prepared in eight steps (18% overall yield) from tricyclic lactam 21 (Scheme XVI). A gratifying level of stereocontrol at position 9 has been achieved via an intermolecular amidoalkylation reaction.

In the course of our synthesis of 93, we have constructed all of the carbon-carbon bonds required for the preparation of naphthyridinomycin A. Furthermore, this intermediate possesses the correct relative stereochemistry and appropriate functionality for its ultimate conversion to the target structure.

There are four remaining transformations which must be accomplished in order to complete the total synthesis (Scheme XVI): (1) reduction of the 9-methoxycarbonyl group; (2) controlled reduction of the lactam carbonyl group [C(7)]; (3) oxidation of the aromatic nucleus; and (4) introduction of the final oxazolidine ring via the methodologies previously discussed (eq 3 and Scheme III). It is hoped that with the aid of the research described herein, the total synthesis of the complex antibiotic naphthyridinomycin A will be accomplished in the near future.

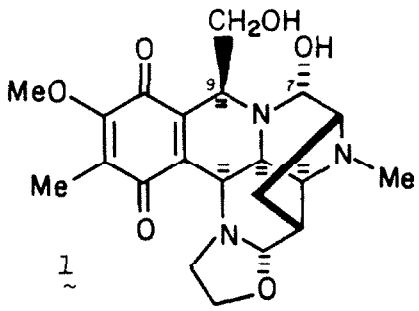
Scheme XVI

Summary



93

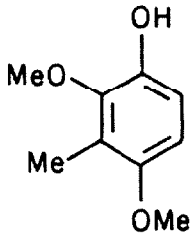
8 steps | 18%



1

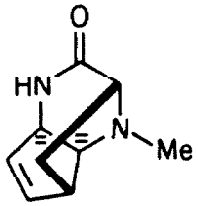
Naphthyridinomycin A

Average yield per step: 85%



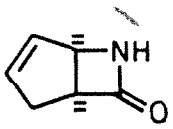
19a

CO_2Me
CHO



21

13 steps
18%



31

V. Experimental Section

General. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4210 spectrophotometer. Unless otherwise stated, ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in ppm on the δ scale from internal tetramethylsilane for organic solvents and from sodium 3-(trimethylsilyl)propanoate in deuterium oxide (D_2O). Unless presented in tabular form, ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant (Hz) and interpretation. 500 MHz ^{1}H NMR spectra were recorded on the Bruker WM-500 spectrometer at the Southern California Regional NMR Facility under National Science Foundation Grant Number CHE-7916324. ^{1}H NMR-variable temperature studies were performed on a JOEL-FX-90Q (90 MHz) spectrometer. ^{13}C NMR spectra were recorded on a Varian Associates XL-100 (25.2 MHz) or a JOEL-FX-90Q (22.5 MHz) spectrometer and are reported in ppm from tetramethylsilane on the δ scale. When

multiplicities were determined on the ^{13}C spectra (by off resonance decoupling), they are reported using the abbreviations given above. Mass spectral analyses were performed by the California Institute of Technology Microanalytical Laboratory on a Dupont 21-492 B spectrometer, and by the Midwest Center for Mass Spectrometry at the University of Nebraska, Lincoln, on a Kratos MS-50 TA spectrometer. Combustion analyses were performed by the California Institute of Technology Microanalytical Laboratory, Spang Microanalytical Laboratory (Eagle Harbor, Michigan) and Galbraith Laboratories (Knoxville, Tennessee).

Analytical gas-liquid chromatography (GLC) was carried out on a Hewlett Packard 5880A Level 3 gas chromatograph, equipped with a split mode capillary injection system and a flame ionization detector. Unless otherwise indicated, a 10 m methyl silicone column (Hewlett Packard fused silica WCOT 0.21 mM i.d.) was employed. Specific GLC conditions reported are: oven temperature, carrier gas (hydrogen) flow rate, and retention times. Flash chromatography was performed according to the general procedure of Still,[64] employing Merck 40-63 μm silica gel 60 or Whatman 37-53 μm silica gel LPS-2. Medium pressure liquid chromatography was

performed using EM Laboratories LoBar Silica Gel 60 prepacked columns (column size indicated) on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP Lab Pump. Preparative high pressure liquid chromatography was performed on a Waters Associates "Prep 500" equipped with a refractive index detector. Thin-layer chromatography (TLC) was performed using Merck 0.25 mm silica gel 60 plates.

When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran and benzene were distilled from sodium metal/benzophenone ketyl. Pyridine, t-butanol, triethylamine, boron trifluoride etherate, dimethyl sulfoxide, acetonitrile, ethyldiisopropylamine, valerolactam, hexamethylphosphorous triamide [$(Me_2N)_3P$] and 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) were distilled from calcium hydride. Dichloromethane was freshly distilled from calcium hydride or passed through a column of activity I alumina and stored over activated 4 Å sieves. Carbon tetrachloride was dried over activated 4 Å sieves. Methanesulfonyl chloride was distilled from phosphorous pentoxide. Methanol was distilled from magnesium methoxide. Mallinckrodt anhydrous diethyl ether was used directly without purification.

Potassium metal was handled according to the pro-

cedure of Johnson.[81] Potassium t-butoxide was prepared from potassium metal as a solution in t-butanol[81], or commercial material (Aldrich Chemical Co.) was employed after sublimation. Silver(I) trifluoromethanesulfonate was prepared according to the procedure of Whitesides,[59] or commercial material (Aldrich Chemical Co.) was employed after purification by dissolving in acetone, filtering to remove insoluble residues, concentrating in vacuo, and drying at 110°C under vacuum. This hydroscopic substance was stored and handled in a Vacuum Atomspheres Co. dry box under nitrogen. Copper(I) trifluoromethanesulfonate was prepared according to the procedure of Kochi,[56a] and was handled under an argon atmosphere. Polymeric methyl and ethyl glyoxalates were prepared according to the procedure of Kelly.[65]

A gaseous solution of ozone in oxygen was prepared employing a Welsbach ozone generator. Cyclopentadiene was prepared by the cracking of dicyclopentadiene immediately before use. Phenol 19a was prepared according to literature procedures.[11,16]

cis-6-Azabicyclo[3.2.0]hept-3-ene-7-one (31).[19,25] To a stirred solution of 75 mL (0.86 mol) of chlorosulfonyl isocyanate in 1.3 L of ether[25] maintained between -18°C and -21°C under argon was added 90 mL (1.09 mol)

of cyclopentadiene dropwise over 1 h 25 min. After stirring for an additional 1 h 15 min between -21°C and -24°C, the reaction solution was cannulated over 9 min into a rapidly stirred, ice-cooled solution of 252 g (2 mol) of Na_2SO_3 and 483 g (2.1 mol) of $K_2HPO_4 \cdot 3\ H_2O$ in 1 L of water. After 20 min at 0°C, the organic layer was diluted with 500 mL of ethyl acetate and the rapidly stirred mixture was allowed to warm to room temperature for 45 min. The organic layer was separated and the aqueous layer was extracted with two 1.2-L portions of ethyl acetate. An insoluble solid, presumably polymer, floated between the layers during the extraction, and was discarded. The individual extracts were washed with 100 mL of brine, dried (Na_2SO_4), concentrated in vacuo, and then combined to afford 56.2 g of crude 31. ^1H NMR and TLC (95:5 ethyl acetate:methanol) indicated that this material contained none of the undesired [4+2] adduct 32. The crude product was combined with that of a second reaction which had been carried out on the same scale. Simple distillation (73-80°C, 0.09-0.15 mm) afforded 93.2 g (50%) of a pale yellow liquid which solidified upon standing in the cold: mp 32-33°C (lit.[19] oil).

Methyl cis-2-Amino-3-cyclopentene-1-carboxylate

Hydrochloride (33). Anhydrous, gaseous hydrogen chloride was bubbled through a stirred solution of 14.65 g (0.134 mol) of 31 in 250 mL of methanol for 3 min, when the solvent began to boil. The solution was allowed to stir for 20 min at which point TLC (95:5 ethyl acetate: methanol) indicated that no starting material remained. Solvent removal in vacuo afforded a tan solid which was recrystallized from i-propanol/ethyl acetate to yield 21.34 g (90%) of a white, crystalline solid: mp 176-177°C; IR (nujol) 2400-3300, 1720, 1600, 1545, 1500, 1303, 1268, 1205, 1155, 1040, 732 cm^{-1}; ^1H NMR (D_2O) δ 6.27 (m, 1, =C-H), 5.83 (m, 1, =C-H), 4.50 (d of m, 1, J_d = 8 Hz, NCH), 3.77 (s, 3, CH_3), 3.58 (q, 1, J = 8 Hz, O=CCH), 2.80 (d of m, 2, J_d = 8 Hz, CH_2).

Anal. calcd. for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; N, 7.89. Found: C, 47.56; H, 6.46; N, 7.85.

cis-2-Amino-3-cyclopentene-1-methanol (34). Anhydrous, gaseous hydrogen chloride was bubbled through a stirred solution of 92.0 g (0.843 mol) of 31 in 1 L of absolute methanol for 3 min, when the solvent began to boil. After the exotherm subsided, this procedure was repeated twice more, at which point the solution was strongly acidic and TLC (95:5 ethyl acetate:methanol) indicated that no starting material remained. Solvent

removal in vacuo afforded crude 33 as a tan solid: mp 172-173°C.

The crude ammonium salt (33) was partitioned between 3 L of dichloromethane and 500 mL of 2 M aqueous Na_2CO_3. The aqueous layer was separated, diluted with an additional 100-mL portion of 2 M aqueous Na_2CO_3 and extracted with two 1-L portions of dichloromethane. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford 127.3 g of the free amine as a dark liquid. A solution of this crude material in 300 mL of ether was added dropwise over 1 h 45 min to a mechanically stirred suspension of 64.86 g (1.66 mol) of lithium aluminum hydride in 2 L of ether at 0°C under argon. The reaction mixture was allowed to warm to room temperature and stir for 2 h. The stirred suspension was re-cooled to 0°C and slowly and cautiously quenched via the dropwise addition of 65 mL of water, 65 mL of 15% aqueous NaOH and finally 200 mL of water. The granular suspension was allowed to gradually warm to room temperature while stirring for 10 h. Some anhydrous Na_2SO_4 was added and the salts were removed by filtration through celite. The filter cake was washed with ether followed by dichloromethane, and the filtrate was concentrated in vacuo to yield 95.6 g of a dark liquid.

Simple distillation (65-68°C, 0.15-0.20 mm) afforded 85.06 g (89% from 31) of a nearly colorless liquid which solidified upon standing in the cold to give a hydroscopic white solid: mp 29-31°C; IR (neat) 3300, 2920, 2840, 1570, 1440, 1380, 1030, 955, 720 cm^{-1}; ^1H NMR ($CDCl_3$, concentrated) δ 5.73 (m, 2, =C-H), 4.03 (d of m, 1, J_d = 6 Hz, NCH), 3.65 (d, 2, J = 7 Hz, OCH_2), 2.73 (s, 3, OH and NH_2), 1.9-2.7 (m, 3, $=CCH_2$ OCCH); ^{13}C NMR ($CDCl_3$) δ 134.2 (d), 131.6 (d), 63.2 (t), 58.4 (d), 41.3 (d), 38.8 (t).

The ^1H NMR spectrum of 34 exhibited significant concentration dependence. See NMR and IR Spectral Catalog (Appendix I).

The picrate of 34 was prepared and recrystallized from ethanol to afford golden crystals: mp 163.5-165.5°C; ^1H NMR (DMSO-d_6) δ 8.62 (s, 2, aromatic-H), 7.00 (br, 3, NH_3), 6.13 (m, 1, =C-H), 5.72 (m, 1, =C-H), 4.19 (br d, 1, J = 7 Hz, NCH), 3.60 (d, 2, J = 6 Hz, OCH_2), 3.0-4.0 (br, 1, OH), 2.0-2.8 (m, 3, $=C-CH_2$ and OCCH).

Anal. calcd. for $C_{12}H_{14}N_4O_8$: C, 42.11; H, 4.12; N, 16.37. Found: C, 41.98; H, 4.00; N, 16.29.

[cis-2-(Hydroxymethyl)-4-cyclopenten-1-ylamino]-acetonitrile (35a) and Phenylmethyl (Cyanomethyl)[cis-2-(hydroxymethyl)-4-cyclopenten-1-yl]carbamate (35b).

To a solution of 5.51 g (48.7 mmol) of 34 and 3.24 g (66.1 mmol) of sodium cyanide in 100 mL of methanol and 30 mL of water was added 8.24 g (61.0 mmol) of the formaldehyde-sodium bisulfite adduct, causing the precipitation of white crystalline salts. After stirring for 9 h at room temperature, the reaction mixture was partitioned between 500 mL of chloroform and 100 mL of 1 M aqueous NaOH. The aqueous phase was re-extracted with 200 mL of chloroform and the combined organic layers were washed with 100 mL of brine, dried (Na_2SO_4) and concentrated in vacuo to afford 7.86 g of crude 35a as a yellow liquid.

[Intermediate 35a could be purified, albeit with some material loss, by MPLC (98:2 to 95:5 ethyl acetate: methanol) to provide a pale yellow liquid which solidified on standing: mp 38-43°C; IR ($CHCl_3$) 3600, 3100-3600, 3050, 3000, 2930, 2850, 2240, 1611, 1440, 1413, 1358, 1210, 1125, 1085, 1030, 950, 905, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.91 (br s, 2, =C-H), 3.96 (br d, 1, J = 7 Hz, NCH), 3.65 (d, 2, J = 7.5 Hz, OCH_2), 3.61 (s, 2, NCH_2), 1.7-3.0 (m, 5, OH, NH, =C-CH_2, OCCH); mass spectrum m/z (rel. intensity) 152 (2.7, parent ion), 125 (20), 124 (19), 121 (41), 95 (52), 94 (66.8), 80 (45), 79 (61), 68 (27), 67 (71), 66 (100), 65 (26), 41 (59), 40 (29),

39 (68).]

To a stirred solution of the crude 35a and 17.5 mL (100 mmol) of ethyl diisopropylamine in 250 mL of dichloromethane under argon at 0°C was added 9.5 mL (53.6 mmol) of benzyloxycarbonyl chloride (80% pure by ^{1}H NMR) dropwise over 10 min. After stirring for 1 h at 0°C, the solution was diluted with 250 mL of dichloromethane and washed with 100-mL portions of 1 M aqueous HCl, saturated aqueous $NaHCO_3$ and brine. Drying (Na_2SO_4) and concentration in vacuo gave a yellow oil, which was purified by flash chromatography on 175 g of silica gel (60:40 ethyl acetate:hexanes followed by 75:25 ethyl acetate:hexanes) to afford 12.04 g (86% from 34) of a near colorless oil. An analytical sample was prepared by bulb-to-bulb distillation (225°C, 0.01 mm) to afford a thick, colorless oil: IR ($CHCl_3$) 3200-3600, 3060, 2940, 1693, 1490, 1425, 1400, 1355, 1320, 1250, 1173, 1125, 1030, 905 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 5, aromatic -H), 6.23 (m, 1, =C-H), 5.83 (m, 1, =C-H), 5.23 (br s, 3, $PhCH_2$ and NCH), 4.17 (br d, 1, J = 17 Hz, NCH_2), 3.73 (d, 1, J = 17 Hz, NCH_2), 3.57 (br d, 2, J = 6 Hz, $HOCH_2$), 1.8-3.0 (m, 4, OH, =C-CH_2, OCCH).

Anal. calcd. for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.26; H, 6.20; N, 9.80.

Phenylmethyl (Cyanomethyl) [cis-2-[[[(4-methylphenyl)-sulfonyl]oxy]methyl]-4-cyclopenten-1-yl]carbamate (36).

To a solution of 78.65 g (0.695 mol) of 34 and 45.2 g (0.92 mol) of sodium cyanide in 350 mL of methanol and 175 mL of water was added 116.5 g (0.87 mol) of formaldehyde-sodium bisulfide adduct, causing the precipitation of white crystalline salts. After stirring for 4 h 15 min at room temperature, the salts were removed by filtration and washed with dichloromethane. The filtrate was partitioned between 2 L of dichloromethane and 80 mL of 15% aqueous NaOH, and the aqueous layer was re-extracted with 2 L of dichloromethane. The combined organic layers were washed with 150 mL of brine, dried (Na_2SO_4) and concentrated in vacuo to afford 109.4 g of crude 35a as a dark liquid.

To a stirred solution of the crude 35a and 181 mL (1.04 mol) of ethyldiisopropylamine in 1.7 L of dichloromethane under argon at 0°C was added 121 mL (0.77 mol) of benzyloxycarbonyl chloride (90% pure by ^1H NMR, 10% benzyl chloride) dropwise over 0.5 h. After stirring for 1 h at 0°C, the solution was washed with 200-mL portions of 10% aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated in vacuo to afford 227.6 g of crude 35b as a dark, thick oil.

To a solution of the crude 35b in 750 mL of pyridine at 0°C was added 267 g (1.4 mol) of p-toluenesulfonyl chloride. The reaction was allowed to stand at 5°C for 12 h when it was poured onto 800 g of ice and swirled until the ice had melted. The crude product was extracted with two 1-L portions of dichloromethane, and the combined organic layers were washed with two 1-L portions of 6 N aqueous HCl, 500 mL of 9% aqueous NaOH, and 400 mL of brine. Drying ($MgSO_4$, activated charcoal) and concentration in vacuo afforded 295.7 g of a red semisolid. Recrystallization from ethanol yielded 218.5 g (71%, overall from 34) of an off-white solid: mp 77-78°C.

In a separate experiment, p-toluenesulfonation of 12.0 g (42 mmol) of chromatographically purified 35b as described above, afforded, after recrystallization of the crude product from ether/hexanes, 15.55 g (84%) of a white solid: mp 77-78°C; IR ($CHCl_3$) 3020, 2950, 1700, 1595, 1428, 1400, 1360, 1250, 1185, 1172, 970, 950, 935 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (d, 2, J = 8.5 Hz, tosyl aromatic-H), 7.39 (s, 5, benzyl aromatic-H), 7.30 (d, 2, J = 8.5 Hz, tosyl aromatic-H), 6.14 (m, 1, =C-H), 5.80 (m, 1, = C-H), 5.16 (br s, 3, $PhCH_2$ and NCH), 4.12 (d, 1, J = 18 Hz, NCH_2), 4.02 (m, 2, $SOCH_2$), 3.60 (d, 1, J = 18 Hz, NCH_2), 2.0-3.0 (m, 6, = $C-CH_2$, OCCH and CH_3 singlet at δ 2.42).

Anal. calcd. for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36. Found: C, 62.76; H, 5.40; N, 6.39.

Phenylmethyl (2α,3aα,6aα)-2-Cyano-3,3a,4,6a-tetrahydro-1(2H)-cyclopenta[b]pyrrolecarboxylate (38) and the Corresponding (2α,3aβ,6aβ)-Isomer (39). A 2-L, three-necked flask, fitted with an addition funnel and a mechanical stirrer, was maintained under argon and charged with a solution of 46.5 g (0.105 mol) of 36 in 500 mL of tetrahydrofuran. A solution of potassium t-butoxide, prepared from 4.37 g (0.11 mol) of potassium metal and 90 mL of t-butanol,[81] was transferred via cannula into the addition funnel, with the aid of two 20-mL portions of tetrahydrofuran. While stirring, the potassium t-butoxide solution was added dropwise over 50 min at room temperature, resulting in the precipitation of much white solid. After an additional 25 min, the suspension was poured into 200 mL of water and 100 mL of saturated aqueous NH_4Cl. The crude product was extracted with 750 mL of ether, and the organic layer was washed with 200 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford 29.68 g of a pale orange oil. TLC (35:65 ethyl acetate:hexanes) and ^1H NMR indicated that this was a mixture of 38 and 39. The ratio of 38:39 was determined to be 60:40 by GLC [190°C, 29.2 cm/sec,

RT(38) = 6.29 min, RT(39) = 6.83 min].

The isomeric mixture was separated on the Water's "Prep 500",[27] employing two Water's "PrepPAK" silica gel cartridges, equilibrated and eluted with 12:88 ethyl acetate:hexanes. Approximately 1-L fractions were collected at a flow rate of 0.25 L min^{-1}. Fractions 5-8 afforded 16.16 g (57.5%) of pure 38 as a white solid, and fractions 9-16 afforded 10.57 g (37.5%) of pure 39 as a colorless oil. An analytical sample of 39 was prepared via bulb-to-bulb distillation (210-220°C, 0.2-0.3 mm).

38: mp 52-54.5°C; IR ($CHCl_3$) 3020, 2960, 2930, 2865, 2240, 1710, 1450, 1410, 1353, 1278, 1205, 1122, 1100, 1065, 1022, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, see Table 5); ^{13}C NMR ($CDCl_3$, two carbamate rotomers) δ 153.9, 153.4, 136.1, 131.3, 131.1, 130.3, 130.0, 128.5, 128.1, 127.9, 118.7, 68.8, 68.0, 67.5, 48.1, 47.7, 39.4, 38.3, 37.0, 36.5, 36.0; mass spectrum m/z (rel. intensity) 268 (1.4), 242 (2.2), 152 (12), 108 (15), 92 (10), 91 (100), 79 (9), 65 (13).

Anal. calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.49; H, 6.12; N, 10.58.

39: IR ($CHCl_3$) 3030, 2960, 2865, 2240, 1708, 1450, 1412, 1360, 1278, 1158, 1120, 995, 695 cm^{-1}; ^1H NMR

($CDCl_3$, 500 MHz, see Table 6); ^{13}C NMR ($CDCl_3$) δ 153.5, 136.1, 133.6, 129.7, 128.5, 128.2, 127.9, 119.1, 68.9 (br), 67.6, 46.6, 39.9 (br), 38.8, 36.7 (br); mass spectrum m/z (rel. intensity) 268 (1.4), 242 (1.5), 152 (9), 108 (14), 92 (10), 91 (100), 79 (10), 65 (13).

Anal. calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.59; H, 5.99; N, 10.51.

Equilibration of Bicyclic Nitriles 38 and 39. (a) Starting from 38. To a stirred solution of 4.6 mg (0.041 mmol) of potassium t-butoxide in 2 mL of t-butanol under argon at room temperature was added a solution of 234.4 mg (0.873 mmol) of 38 in 3 mL of tetrahydrofuran dropwise over 2 min. At the indicated time periods after completion of the addition, 0.2-mL aliquots were removed, partitioned between 10 mL of dichloromethane and 1 mL of saturated aqueous NH_4Cl, dried ($MgSO_4$) and concentrated in vacuo to afford colorless oils which were analyzed by GLC [190°C, 29.7 cm/sec, RT(38) = 6.27 min, RT(39) = 6.81 min]: 5 min, 38:39 = 1.47:1; 20 min, 38:39 = 1.45:1. After stirring for a total of 1 h at room temperature, the remainder of the solution was partitioned between 40 mL of dichloromethane and 5 mL of saturated aqueous NH_4Cl. The aqueous layer was re-extracted with 10 mL of dichloromethane and the combined organic layers

were dried ($MgSO_4$) and concentrated in vacuo to afford 202.5 mg (86%) of a colorless oil. ^1H NMR and TLC (80:20 benzene:ethyl acetate) confirmed that this material was a mixture of 38 and 39. GLC (as above) indicated that the ratio of 38:39 was 1.46:1.0.

(b) Starting from 39. The procedure in part (a) was repeated employing 4.6 mg (0.041 mmol) of potassium t-butoxide and 257.8 mg (0.96 mmol) of 39. Aliquots were processed as above and analyzed by GLC: 5 min, 38:39 = 1.49:1.0; 15 min, 38:39 = 1.48:1.0. After stirring for a total of 1 h at room temperature, the remainder of the solution was worked up as in part (a) to afford 230.2 mg (90%) of a colorless oil. ^1H NMR and TLC confirmed that this material was a mixture of 38 and 39. GLC indicated that the ratio of 38:39 was 1.45:1.0.

Preparative Equilibration - Recycle of 38. To a stirred solution of 16.08 g (59.9 mmol) of 38 in 100 mL of tetrahydrofuran and 100 mL of t-butanol under argon was added 0.48 g (4.3 mmol) of potassium t-butoxide in 15 mL of tetrahydrofuran. After 35 min at room temperature, the yellow solution was partitioned between 500 mL of ether and 200 mL of 1:1 saturated aqueous NH_4Cl:water. The organic layer was dried ($MgSO_4$) and

concentrated in vacuo to afford 16.8 g of a pale yellow oil. GLC [190°C, 29.7 cm/sec, RT(38) = 6.30 min, RT(39) = 6.84 min] indicated that the ratio of 38:39 was 1.45:1.0. This isomeric mixture was separated on the Water's "Prep 500",[27] employing two Water's Prep PAK silica gel cartridges, equilibrated and eluted with 13:87 ethyl acetate:hexanes. Approximately 1-L fractions were collected at a flow rate of 0.25 L min^{-1}. Fractions 5-7 afforded 8.64 g (54%) of pure 38 as a white solid (mp 52.5-54.5°C), and fractions 8-13 afforded 5.76 g (36%) of pure 39 as a nearly colorless oil.

Phenylmethyl (1aα,2aβ,4α,5aβ,5bα)-4-Cyanohexahydro-5(1aH)-oxireno[4,5]cyclopenta[1,2-b]pyrrolecarboxylate (40) and the Corresponding (1aα,2aα,4β,5aα,5bα)-Isomer (41).

To a stirred solution of 12.52 g (47.0 mmol) of 39 in 150 mL of dichloromethane under argon was added 15.0 g (70.0 mmol) of m-chloroperbenzoic acid (80% purity). After 23 h at room temperature, the precipitated m-chlorobenzoic acid was removed by filtration and the solids were washed with dichloromethane. The filtrate was diluted to 300 mL with dichloromethane, and washed with 50 mL of saturated aqueous Na_2SO_3, 75 mL of 2 M aqueous Na_2CO_3 and 50 mL of brine. Drying ($MgSO_4$) followed by concentration in vacuo afforded 14.7 g of a thick oil.

GLC [220°C, 30.3 cm/sec, RT(40) = 3.43 min, RT(41) = 5.10 min] indicated that epoxides 40 and 41 were formed in a 91:9 ratio, respectively. The mixture of epoxides was separated by flash chromatography on 200 g of silica gel. Approximately 100-mL fractions were collected, eluting with 50:50 ethyl acetate:hexanes (fractions 1-12) followed by 70:30 ethyl acetate:hexanes (fractions 13-21). Fractions 6-9 afforded 11.74 g (88%) of pure 40 as a thick oil; fractions 10 and 11 afforded 0.19 g (1.4%) of a 79:21 mixture (GLC) of 40:41; fractions 12-19 afforded 1.16 g (8.7%) of pure 41 as a white solid. An analytical sample of 40 was prepared by bulb-to-bulb distillation (250°C, 0.012-0.015 mm).

40: IR ($CHCl_3$) 3030, 2960, 2240, 1712, 1450, 1410, 1350, 1285, 1215, 1110, 1080, 1030, 990, 975, 905, 845, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37 (s, 5, aromatic-H), 5.21 (s, 2, OCH_2), 4.79 (m, 1, NCH), 4.34 (d, 1, J = 7 Hz, NCH), 3.86, 3.69 and 3.59 (br, 2 protons total, OCH), 1.7-2.9 (m, 5, CH_2CHCH_2).

Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.35; H, 5.60; N, 9.82.

41: mp 110-112.5°C; IR ($CHCl_3$) 3035, 2960, 2245, 1710, 1450, 1412, 1368, 1332, 1283, 1220, 1168, 1125, 1080, 1020, 975, 850, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37

(s, 5, aromatic-H), 5.21 (s, 2, OCH_2), 4.2-4.7 (m, 2, NCH), 3.69 and 3.59 (br, 2 protons total, OCH), 1.9-2.9 (m, 5, CH_2CHCH_2).

Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.19; H, 5.58; N, 9.93.

Phenylmethyl (1aα,2aβ,4α,5aβ,5bα)-4-(Aminocarbonyl)-hexahydro-5(1aH)-oxireno[4,5]cyclopenta[1,2-b]pyrrole-carboxylate (42). To a stirred solution of 11.23 g (39.5 mmol) of 40 in 220 mL of acetone was added 18.1 mL (160 mmol) of 30% aqueous hydrogen peroxide and 40 mL of 2 M aqueous Na_2CO_3 to afford a white suspension. After 0.5 h at room temperature, the reaction mixture was heated to reflux for 1.5 h, and then cooled to 0°C. Saturated aqueous Na_2SO_3 (150 mL) was added followed by warming to room temperature. The reaction mixture was partitioned between 500 mL of dichloromethane and 100 mL of water, and the aqueous layer was re-extracted with 500 mL of dichloromethane. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford 11.7 g of a white solid. Recrystallization from dichloromethane/hexanes gave 10.88 g (91%) of a white solid: mp 154-155°C; IR ($CHCl_3$) 3200-3500, 3010, 1685, 1585, 1565, 1448, 1403, 1350, 1280, 1210, 1110, 842, 692 cm^{-1}; ^1H NMR ($CDCl_3$)

δ 7.36 (s, 5, aromatic-H), 6.53 (br, 1, NH), 6.06 (br, 1, NH), 5.20 (s, 2, OCH_2), 4.52 (m, 1, O=CCHN), 4.40 (d, 1, J = 6.5 Hz, O-CCHN), 3.68 (br s, 1, OCH), 3.47 (br s, 1, OCH), 1.4-2.9 (m, 5, CH_2CHCH_2); ^{13}C NMR ($CDCl_3$) δ 174.7, 155.6, 135.7, 128.5, 128.2, 127.9, 67.8, 64.9, 61.9, 58.3, 38.6 (br), 32.5 (br), 31.2 (br).

Anal. calcd. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.38; H, 5.93; N, 9.18.

Phenylmethyl (1aα,2aβ,4β,5aβ,5bα)-4-Cyanohexahydro-5(1aH)-oxireno[4,5]cyclopenta[1,2-b]pyrrolecarboxylate (43) and the Corresponding (1aα,2aα,4α,5aα,5bα)-Isomer (44). (a) Employing m-Chloroperbenzoic Acid. To a stirred solution of 279 mg (1.04 mmol) of 38 in 4 mL of dichloromethane under argon was added 357 mg (1.65 mmol) of m-chloroperbenzoic acid (80% purity). After 25 h at room temperature, the reaction mixture was diluted with dichloromethane, washed with saturated aqueous Na_2SO_3, 1 M aqueous Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated in vacuo to afford 297 mg of a colorless oil. GLC [200°C, 36.2 cm/sec, RT(43) = 6.33 min, RT(44) = 6.70 min] indicated that epoxides 43 and 44 were formed in a 74:26 ratio, respectively. The mixture of epoxides was separated by MPLC (LoBar size B column, 35:65 ethyl acetate:hexanes followed by 45:55 ethyl

acetate:hexanes) to provide 201.4 mg (68%) of the less polar component 43 as a white solid, and 75 mg (25%) of the more polar component 44 as a colorless oil.

43: mp 106-108°C; IR ($CHCl_3$) 3020, 2950, 1702, 1490, 1443, 1408, 1350, 1269, 1249, 1215, 1120, 1095, 845, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (s, 5, aromatic-H), 5.21 (s, 2, OCH_2), 4.68 (m, 1, NCH), 4.28 (m, 1, NCH), 3.81 (br s, 0.5, OCH), 3.56 (br s, 1.5, OCH), 2.91 (m, 1, CH_2CHCH_2), 1.8-2.3 (m, 4, CH_2CHCH_2).

Exact mass calcd. for $C_{16}H_{16}N_2O_3$: 284.1161. Found: 284.1158.

44: IR ($CHCl_3$) 3020, 2955, 1705, 1493, 1445, 1408, 1352, 1335, 1277, 1210, 1170, 1130, 1108, 970, 840, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (s, 5, aromatic-H), 5.21 (br s, 2, OCH_2), 4.51 (t, 1, J = 7 Hz, NCH), 4.27 (d, 1, J = 7 Hz, NCH), 3.5-4.0 (br, 1, OCH), 3.44 (m, 1, OCH), 2.76 (m, 1, CH_2CHCH_2), 1.7-2.6 (m, 3, CH_2CHCH_2), 1.49 (d of d of d, 1, J = 14 Hz, 5 Hz and 2 Hz, CH_2CHCH_2).

Exact mass calcd. for $C_{16}H_{16}N_2O_3$: 284.1161. Found: 284.1160.

(b) Employing Peroxytrifluoroacetic Acid. A solution of peroxytrifluoroacetic acid was prepared as follows:[82] To a stirred suspension of 0.04 mL (1.32 mmol) of 90% aqueous hydrogen peroxide in 2 mL of dichloro-

methane at 0°C was added 0.22 mL (1.58 mmol) of trifluoroacetic anhydride. After 50 min at 0°C, this solution was added dropwise over 18 min to a stirred suspension of 118 mg (0.44 mmol) of 38 and 580 mg (5.5 mmol) of anhydrous Na_2CO_3 in 5 mL of dichloromethane, cooled between -18°C and -15°C and protected with a $CaSO_4$ drying tube. After 1.7 h at this temperature, the stirred suspension was allowed to warm to 0°C for 1.7 h, when it was quenched with 8 mL of 1:1 saturated aqueous Na_2SO_3:water. The crude product was extracted with 40 mL of dichloromethane, dried (Na_2SO_4) and concentrated in vacuo to afford 124.7 mg (99%) of a colorless oil. ^1H NMR and TLC (50:50 ethyl acetate:hexanes) were consistent with a clean mixture of epoxides 43 and 44. GLC [22 m methyl silicone column, 230°C, 23.7 cm/sec, RT(43) = 7.82 min, RT(44) = 8.08 min] indicated that 43 and 44 were formed in a ratio of 68:32, respectively.

Phenylmethyl (2α,4aβ,5β,7α,7aβ)-Octahydro-5-hydroxy-3-oxo-2,7-methano-1H-cyclopentapyrazine-1-carboxylate (45) and Phenylmethyl (2α,3aβ,5α,6β,6aβ)-Hexahydro-6-hydroxy-8-oxo-5,2-(iminomethano)cyclopenta-[b]pyrrole-1(2H)-carboxylate (46). To a stirred solution of 0.41 g (3.64 mmol) of potassium t-butoxide in 30 mL of t-butanol at room temperature under argon was added

0.95 g (3.1 mmol) of epoxy amide 42. After stirring for 2 h, the reaction solution was diluted with 100 mL of ether, washed with 20 mL of 1:1 saturated aqueous NH_4Cl:water and 20 mL of brine, dried ($MgSO_4$) and concentrated in vacuo to afford 1.02 g of a mixture of lactams 45 and 46. This mixture was separated by MPLC (LoBar size B column), collecting 8 mL fractions and eluting with dichloromethane (fractions 1-5), 93:7 dichloromethane:methanol (fractions 6-52) and finally 90:10 dichloromethane:methanol (fractions 53-80). Fractions 36-43 afforded 0.404 g (42.5%) of 46 as a white foam and fractions 45-65 afforded 0.439 g (46.2%) of 45 as a white solid.

45: mp 133-135°C; IR ($CHCl_3$) 3150-3650, 3010, 2960, 1680, 1490, 1450, 1415, 1362, 1310, 1290, 1270, 1250, 1210, 1169, 1148, 1100, 1055, 975, 750, 720, 690 cm^{-1}; ^1H NMR ($CDCl_3$, see Table 8); ^{13}C NMR ($CDCl_3$) δ 173.3, 154.2, 136.0, 128.6, 128.2, 127.9, 76.6, 67.5, 60.6, 60.3, 58.9, 39.9, 37.0.

Anal. calcd. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.39; H, 5.84; N, 9.24.

46: IR ($CHCl_3$) 3600, 3100-3550, 3010, 2975, 1665 (shoulder at 1685), 1490, 1450, 1415, 1360, 1314, 1288, 1210, 1103, 955, 935, 690 cm^{-1}; ^1H NMR ($CDCl_3$, see

Table 8); ^{13}C NMR ($CDCl_3$) δ 177.5, 153.5, 136.3, 128.4, 128.0, 127.4, 79.8, 78.6, 67.7, 67.2, 61.6, 58.7, 39.8, 39.3, 36.6.

Anal. calcd. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.48; H, 5.94; N, 9.22.

(1aα,2aβ,4α,5aβ,5bα)-Hexahydro-4(1aH)-oxireno[4,5]-cyclopenta[1,2-b]pyrrolecarboxamide (47a). A stirred suspension of 753 mg (2.49 mmol) of 42 and 75 mg of 10% palladium on carbon in 50 mL of methanol was hydrogenated at room temperature and atmospheric pressure for 20 min. The catalyst was removed by filtration through celite, and the filtrate was concentrated in vacuo to afford 429 mg of a white solid. Recrystallization from chloroform/hexanes gave 347 mg (83%) of colorless needles: mp 146-148°C; IR ($CHCl_3$) 3500, 3360, 3000, 1675, 1540, 1110, 1018, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (br, 1, NH), 6.12 (br, 1, NH), 3.93 (d, 1, J = 7.5 Hz, O-CCHN), 3.83 (m, 1, O=CCHN), 3.43 (s, 2, OCH), 1.8-2.8 (m, 5, CH_2CHCH_2, NH), 1.43 (d of d of d, 1, J = 13 Hz, 6 Hz, and 1 Hz, CH_2CHCH_2).

Anal. calcd. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.98; H, 7.13; N, 16.54.

(1aα,2aβ,4α,5aβ,5bα)-Hexahydro-5-methyl-4(1aH)-oxireno[4,5]cyclopenta[1,2-b]pyrrolecarboxamide (47b).[33] A stirred suspension of 4.14 g (13.7 mmol) of 42 and

0.60 g of 5% palladium on carbon in 180 mL of methanol was hydrogenated at room temperature and atmospheric pressure until 233 mL (10.4 mmol, 0.76 equiv) of hydrogen had been consumed (0.5 h) and TLC (90:10 dichloromethane: methanol) indicated that 42 had been cleanly converted to 47a. The hydrogen atmosphere was replaced with nitrogen, and 1.2 mL (16 mmol) of 37% aqueous formaldehyde was added. After stirring for 1 h, TLC (as above) indicated that intermediate 47c (R = CH_2OMe) had formed. [The structure of intermediate 47c had been assigned by ^1H NMR in the course of previous experiments: ^1H NMR ($CDCl_3$) δ 7.27 (br, 1, NH), 6.25 (br, 1, NH), 4.20 (s, 2, OCH_2N), 3.6-4.0 (m, 2, NCH), 3.49 (s, 2, OCH), 3.30 (s, 3, CH_3), 1.8-2.9 (m, 4, CH_2CHCH_2), 1.47 (d of d, 1, J = 14 Hz and 7 Hz, CH_2CHCH_2).]

Hydrogenation (1 atm) was resumed until 310 mL (13.8 mmol, 1.01 equiv) of hydrogen was consumed (1 h 10 min). An 0.5-mL aliquot was removed, filtered through celite, evaporated and analyzed by ^1H NMR, which indicated that a trace of 47c remained. (Note that 47b and 47c cospot on TLC and consequently, ^1H NMR was the most convenient method to monitor the progress of this reaction.) Thus, the stirred suspension was hydrogenated (1 atm) for an additional 10 min during which a final

5 mL of hydrogen was absorbed. The catalyst was removed by filtration through celite, the filter cake was washed with dichloromethane and the filtrate was evaporated at reduced pressure to afford a thick oil. This material was dissolved in chloroform, dried (Na_2SO_4) and concentrated in vacuo to give 2.6 g of a white solid. The crude product was purified by flash chromatography on 140 g of silica gel (packed in 97:3 dichloromethane:methanol, eluted with 93:7 dichloromethane:methanol) to yield 2.37 g (95%) of a pure, white solid: mp 123.5-125.5°C; IR ($CHCl_3$) 3100-3700 (including: 3660, 3500, 3430, 3375), 3000, 2860, 2800, 2460, 1680, 1550, 1450, 1395, 1220, 1162, 1078, 1007, 838, 650 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, see Table 7); ^{13}C NMR ($CDCl_3$) δ 177.1, 73.1, 72.4, 58.9, 58.1, 41.2, 38.6, 36.3, 35.2.

Anal. calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.75; N, 15.38. Found: C, 59.24; H, 7.51; N, 15.43.

(2α,4aβ,5β,7α,7aβ)-Octahydro-5-hydroxy-1-methyl-2,7-methano-3H-cyclopentapyrazin-3-one (48b). (a) Via Cyclization of 47b. To a solution of potassium t-butoxide, prepared from 0.63 g (16.1 mmol) of potassium and 150 mL of t-butanol,[81] at 30 °C under argon was added 2.00 g (11.0 mmol) of epoxy-amide 47b. The solution was allowed to stir for 20 h between 30°C and

32°C, at which point TLC (90:10 dichloromethane:methanol, saturated with ammonia gas) revealed that epoxy amide 47b had been consumed and that only a trace of the undesired seven-membered lactam 49b was present. Glacial acetic acid (9.2 mL, 16.1 mmol) was added and the reaction mixture was concentrated in vacuo. The oily residue was dissolved in 3 mL of 1 M aqueous NaOAC and 5 mL of brine, and the aqueous solution was transferred to a continuous extractor with the aid of some chloroform. The aqueous layer was continuously extracted with refluxing chloroform under argon for 24 h, and the organic layer was dried (Na_2SO_4) and evaporated in vacuo to afford a yellow-white solid. The solid was triturated with 30 mL of boiling chloroform, and 25 mL of hexanes were added to induce complete crystallization. After standing at 5°C for 12 h, the crystals were collected, washed with 1:2 dichloromethane:hexanes, and dried at 56°C under vacuum to afford 1.64 g (82%) of a white solid (mp 165-168°C). An analytical sample was prepared by recrystallization from chloroform/hexanes: mp 167-170°C, IR (nujol) 3370, 3175, 1655, 1340, 1310, 1252, 1152, 1130, 1072, 1032 cm^{-1}; ^1H NMR (D_2O, 500 MHz, see Table 8); ^{13}C NMR (D_2O) δ 178.1, 79.1, 68.6, 66.9, 60.7, 41.9, 41.7, 39.0, 38.5.

Anal. calcd. for $C_9H_{14}N_2O_2$: C, 59.23; H, 7.75; N, 15.38. Found: C, 59.46; H, 7.68; N, 15.48.

(b) Via Hydrogenolysis-methylation of 45. A stirred suspension of 168.6 mg (0.56 mmol) of 45, 0.21 mL (2.8 mmol) of 37% aqueous formaldehyde, and 40 mg of 5% palladium on carbon in 5 mL of ethanol was hydrogenated for 45 min at room temperature and atmospheric pressure. The catalyst was removed by filtration through celite and the filtrate was evaporated at reduced pressure. The residue was dissolved in chloroform, dried (Na_2SO_4) and concentrated in vacuo to afford 113 mg of 48b, which was identical to that obtained from 47b by ^1H NMR and TLC (90:10 dichloromethane: methanol, saturated with anhydrous ammonia gas).

(2α, 3aβ, 5α, 6β, 6aβ)-Octahydro-6-hydroxy-1-methyl-5,2-(iminomethano)cyclopenta[b]pyrrol-8-one (49b). A stirred suspension of 155.7 mg (0.515 mmol) of 46, 0.21 mL (2.8 mmol) of 37% aqueous formaldehyde and 40 mg of 5% palladium on carbon in 5 mL of ethanol was hydrogenated for 1 h at room temperature and atmospheric pressure. The catalyst was removed by filtration through celite, and the filtrate was evaporated at reduced pressure, dissolved in chloroform, dried (Na_2SO_4) and concentrated in vacuo to afford 103.5 mg of a thick oil. The crude product was purified

by flash chromatography on 7 g of silica gel (80:10:10 dichloromethane:methanol:triethylamine) to give 88.6 mg (94%) of an off-white solid (mp 148-155°C). An analytical sample was prepared by recrystallization from acetonitrile to yield white crystals mp 159-161°C; IR (nujol) 3250, 1650 (shoulder at 1625), 1310, 1190, 1055, 1015, 963, 940 cm^{-1}; ^{1}H NMR (D_2O, 500 MHz, see Tabel 8); ^{13}C NMR (D_2O) δ 184.3, 75.3, 74.6, 71.1, 60.9, 42.5, 41.2, 38.6.

Anal. calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.75; N, 15.38. Found: C, 58.98; H, 7.61; N, 15.17.

Phenylmethyl (2α,4aβ,7α,7aβ)-Octahydro-3,5-dioxo-2,7-methano-1H-cyclopentapyrazine-1-carboxylate (50). To the dark red solution prepared by stirring 127 mg (1.27 mmol) of chromium trioxide and 0.21 mL (2.64 mmol) of pyridine in 5 mL of dichloromethane for 0.5 h at room temperature was added 670 mg of celite followed by 67.0 mg (0.22 mmol) of 45. After stirring for 45 min, the reaction mixture was filtered, and the filter cake was rinsed thoroughly with dichloromethane (40 mL). The filtrate was washed with 5-mL portions of 10% aqueous NaOH, 1 M aqueous HCl, and saturated aqueous $NaHCO_3$, dried ($MgSO_4/K_2CO_3$) and concentrated in vacuo to afford 47.7 mg (72%) of a colorless oil: IR ($CHCl_3$) 3390,

3010, 2950, 1750, 1690 (shoulder at 1705), 1452, 1408, 1331, 1308, 1292, 1210, 1147, 1105, 1020, 920, 695 cm^{-1}; ^1H NMR ($CDCl_3$, see Table 8); ^{13}C NMR ($CDCl_3$) δ 211.1, 172.0, 154.4, 136.0, 128.6, 128.4, 128.0, 67.8, 59.7, 57.3, 56.4, 41.3, 38.0, 36.3.

Exact mass calcd. for $C_{16}H_{16}N_2O_4$: 300.1110. Found: 300.1107.

(2α,4aβ,5β,7α,7aβ)-Octahydro-5-[(methanesulfonyl)-oxy]-1-methyl-2,7-methano-3H-cyclopentapyrazin-3-one (51). To a stirred suspension of 0.666 g (3.66 mmol) of 48b and 1.5 mL (10.8 mmol) of triethylamine in 35 mL of dichloromethane under argon was added 0.32 mL (4.13 mmol) of methanesulfonyl chloride dropwise over 10 min. After stirring for 40 min at room temperature during which all of the suspended 48b had dissolved, the reaction solution was diluted with 50 mL of chloroform, washed with 15 mL of 1:1 2 M aqueous Na_2CO_3:brine, dried (Na_2SO_4) and concentrated in vacuo to give 1.11 g of a white solid. The crude product was purified by flash chromatography on 40 g of silica gel (90:10 dichloromethane:methanol) to afford 0.90 g (95%) of a white solid: mp 164.5-166°C (dec); IR ($CHCl_3$) 3410, 3040, 2960, 2815, 1680, 1458, 1368, 1343, 1260, 1178, 1155, 1052, 1040, 972, 940, 895, 855, 690 cm^{-1}; ^1H NMR

($CDCl_3$, see Table 8).

Anal. Calcd. for $C_{10}H_{16}N_2O_4S$: C, 46.14; H, 6.20; N, 10.76. Found: C, 45.91; H, 6.12; N, 10.65.

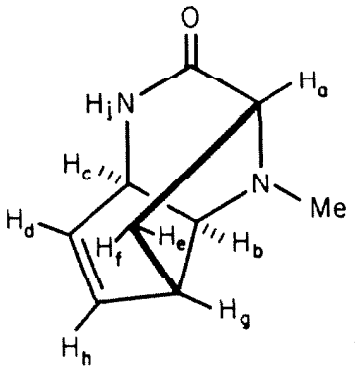
(2α,4aβ,5β,7α,7aβ)-Octahydro-1-methyl-5-(phenylseleno)-2,7-methano-1H-cyclopentapyrazin-3-one (52a). To a stirred suspension of 1.08 g (4.15 mmol) of 51 and 0.78 g (2.5 mmol) of diphenyl diselenide in 40 mL of absolute ethanol under argon at 0°C was added 0.20 g (5.2 mmol) of sodium borohydride portionwise over 5 min, resulting in vigorous hydrogen evolution. After stirring for 15 min at room temperature, an additional "spatula tip" of sodium borohydride was added to completely discharge the yellow color of diphenyl diselenide. The reaction solution was heated to reflux for 2 h, and then partitioned between 200 mL of chloroform and 60 mL of 1:2 2M aqueous Na_2CO_3:brine. The aqueous layer was re-extracted with 50 mL of chloroform, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford a yellow solid. The crude material was purified by flash chromatography on 75 g of silica gel (95:5 dichloromethane:methanol followed by 90:10 dichloromethane:methanol) to give 1.31 g (97%) of a white solid: mp 159-162°C; IR ($CHCl_3$) 3400, 3220, 3085, 3015, 2960, 2810, 1675, 1578, 1480, 1458, 1440, 1312, 1258, 1175, 1140, 1032, 1021, 690 cm^{-1}; ^1H

NMR ($CDCl_3$, 500 MHz, see Table 8); ^{13}C NMR ($CDCl_3$) δ 173.2, 133.8, 129.3, 127.8, 67.3, 64.9, 58.0, 46.9, 39.9, 37.7, 37.4, 36.8.

Anal. calcd. for $C_{15}H_{18}N_2OSe$: C, 57.07; H, 5.65; N, 8.72. Found: C, 55.69; H, 5.89; N, 8.56.

(2α,4aβ,7α,7aβ)-1,2,4,4a,7,7a-Hexahydro-1-methyl-2,7-methano-3H-cyclopentapyrazin-3-one (21). To a solution of 1.27 g (3.97 mmol) of 52a in 10 mL of chloroform was added 0.4 mL (5.2 mmol) of trifluoroacetic acid. After standing for 10 min at room temperature, the solution was concentrated in vacuo and the residue was evaporated with two 10-mL portions of chloroform (to remove the excess CF_3CO_2H) to give a white foam. A solution of the trifluoroacetate salt and 1.8 mL (16.0 mmol) of 90% t-butyl hydroperoxide (Lucidol) in 8 mL of chloroform was allowed to stir at room temperature for 14 h when TLC (85:15 dichloromethane: methanol) of an aliquot (partitioned between ethyl acetate and 10% aqueous NaOH) indicated that all of the phenylselenide 52a had been consumed. The solvent was evaporated at reduced pressure and the oil which remained was maintained under high vacuum for 2 h (in order to remove most of the excess t-butyl hydroperoxide) dissolved in 300 mL of chloroform, washed with 50 mL of

1:1 15% aqueous NaOH:brine followed by 50 mL of 1:1 saturated aqueous Na_2SO_3:brine, dried (Na_2SO_4) and concentrated in vacuo to afford a pale yellow solid. The crude product was purified by flash chromatography on 50 g of silica gel (88:12 dichloromethane:methanol) to yield 0.572 g (88%) of a white solid: mp 146.5-147.5°C; IR ($CHCl_3$) 3410, 3060, 3010, 2950, 2810, 1670, 1450, 1338, 1308, 1245, 1140, 1035, 1012, 875, 850, 692, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.72 (br, 1, H_j), 6.07 (d of d, 1, J_{hg} = 3 Hz, J_{hd} = 6 Hz, H_h), 5.83 (d of d, 1, J_{dc} = 2.5 Hz, J_{dh} = 6 Hz, H_d), 4.09 (d of t, 1, J_{cd} = 2.5 Hz, J_{cj} = 2.5 Hz, J_{cb} = 6 Hz, H_c), 3.82 (t, 1, J_{bc} = 6 Hz, J_{bg} = 6 Hz, H_b), 3.39 (d, 1, J_{ae} = 7.2 Hz, H_a), 3.01 (m, 1, J_{gf} = 3 Hz, J_{gh} = 3 Hz, J_{gb} = 6 Hz, J_{ge} = 10.5 Hz, H_g), 2.56 (s, 3, CH_3), 2.22 (d of d of d, 1, J_{ea} = 7.2 Hz, J_{eq} = 10.5 Hz, J_{ef} = 13 Hz, H_e), 1.47 (d of d, 1, J_{fg} = 3 Hz, J_{fe} = 13 Hz, H_f); ^{13}C NMR ($CDCl_3$) δ 174.2, 137.8, 133.4, 68.1, 66.3, 54.3, 44.7, 36.1, 31.3.



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Anal. calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.78; H, 7.45; N, 17.09.

(2α,3aβ,5α,6β,6aβ)-6-Chlorooctahydro-1-methyl-5,2-(iminomethano)cyclopenta[b]pyrrol-8-one (54b) and (2α,4aβ,6α,7β,7aβ)-7-Chlorooctahydro-1-methyl-2,6-methano-3H-cyclopentapyrazin-3-one (55). To a stirred suspension of 59.6 mg (0.33 mmol) of 49b and 0.14 mL (1.0 mmol) of triethylamine in 4 mL of dichloromethane under argon was added 32 μl (0.41 mmol) of methanesulfonyl chloride dropwise over 4 min. After stirring for 50 min at room temperature during which all of the suspended 49b had dissolved, the solution was diluted with dichloromethane, washed with 1:1 2 M aqueous Na_2CO_3:brine, dried (Na_2SO_4) and concentrated in vacuo to afford 60.2 mg (91%) of a white solid. Although homogeneous by TLC (90:10 dichloromethane:methanol), this material was determined to be a 50:50 mixture of isomeric chlorides 55 and 54b by ^1H NMR ($CDCl_3$). The crude product was purified by flash chromatography on 8 g of silica gel (90:10 dichloromethane:methanol) to give 51.1 mg (77%) of a white solid (mp 150-152.5°C). ^1H NMR ($CDCl_3$) indicated that the ratio of 55:54b immediately after chromatography was 69:31. Within three days in chloroform-d solution at room temperature, the mixture of

isomeric chlorides had reached an equilibrium value of 55:54b = 78:22. Since these isomeric chlorides were inseparable and underwent ready equilibration, the spectral data which are reported here for 54b and 55 have been derived from that of a mixture of the two components: IR ($CHCl_3$) 3425, 3230, 3015, 2985, 2960, 2815, 1683, 1440, 1355, 1328, 1240, 1190, 1172, 1130, 1070, 1040, 1008, 918, 890, 840, 825, 690, 658 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, see Table 8).

Exact mass calcd. for $C_9H_{13}{}^{35}ClN_2O$: 200.072. Found: 200.072.

Ethyl α-Hydroxy-2-oxo-1-piperidineacetate (65). A solution of 1.07 g (10.8 mmol) of valerolactam and 1.95 g (19.1 mmol) of polymeric ethyl glyoxalate[65] in 10 mL of dichloromethane was allowed to stand over 4Å sieves for 5 h at room temperature. The sieves were removed by filtration, and the filtrate was concentrated in vacuo to afford an oil. Flash chromatography on 120 g of silica gel (97.5:2.5 ethyl acetate:methanol) gave 1.79 g (82%) of a white solid: mp 44-46°C; IR ($CHCl_3$) 3150-3700, 3020, 2960, 2880, 1745, 1650, 1496, 1470, 1451, 1420, 1352, 1335, 1305, 1220, 1180, 1100, 1020, 660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52 (d, 1, J = 7 Hz, OCH), 4.59 (d, 1, J = 7 Hz, OH), 4.23 (q, 2, J = 7.5 Hz, OCH_2), 3.37 (m,

2, NCH_2), 2.39 (m, 2, $O{=}CCH_2$), 1.81 (m, 4, $CH_2CH_2CH_2CH_2$), 1.28 (t, 3, J = 7.5 Hz, CH_3).

Exact mass calcd. for $C_9H_{15}NO_4$: 201.1001. Found: 201.0999.

Anal. calcd. for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.73; H, 7. 42; N, 6.88.

Ethyl α-(2-Propylthio)-2-oxo-1-piperidineacetate (66). A solution of 1.59 g (16.0 mmol) of valerolactam (64) and 1.98 g (19.4 mmol) of polymeric ethyl glyoxalate[65] in 10 mL of dichloromethane was allowed to stir for 3 h at room temperature. Magnesium sulfate (2 g) was added, and after an additional 5 h, the reaction mixture was filtered and the filtrate was concentrated in vacuo to afford the crude glyoxalate adduct 65 as a thick oil. To a stirred, two-phase mixture of the crude 65 in 9 mL (96 mmol) of 2-propanethiol and 16 mL of acetic acid at 0°C was added 1.6 mL of concentrated sulfuric acid. After 10 min at 0°C, the reaction mixture was allowed to warm to room temperature, and within 1 h, one homogeneous phase had formed. After stirring for 3.5 h at room temperature, the solution was dissolved in 200 mL of ethyl acetate and the organic layer was washed with 30 mL of water, three 25-mL portions of saturated aqueous $NaHCO_3$, and 30 mL of brine, dried

($MgSO_4$) and concentrated in vacuo to afford 3.6 g of a yellow liquid. Purification by MPLC (LoBar size C column, 50:50 ethyl acetate:hexanes) afforded 2.53 g (61%, overall from 64) of a pale yellow liquid: IR ($CHCl_3$) 2960, 2870, 1732, 1630, 1480, 1460, 1446, 1438, 1412, 1370, 1348, 1330, 1297, 1250, 1172, 1160, 1100, 1080, 1023 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (s, 1, NCHS), 4.16 (q, 2, J = 7 Hz, OCH_2), 3.67 (m, 1, NCH_2), 3.30 (m, 1, NCH_2), 2.92 (quintet, 1, J = 6.8 Hz, $SCHCH_3$), 2.43 (m, 2, $O=CCH_2$), 1.82 (m, 4, $CH_2CH_2CH_2CH_2$), 1.1-1.5 (m, 9, $SCH(CH_3)_2$ and OCH_2CH_3).

Exact mass calcd. for $C_{12}H_{21}NO_3S$: 251.124. Found: 251.125.

α-(2-Propylthio)-2-oxo-1-piperidineacetic Acid (67). A solution of 2.48 g (9.56 mmol) of ester 66 in 45 mL of methanol and 20 mL of 15% aqueous NaOH was allowed to stir for 1.5 h at room temperature. The reaction mixture was partitioned between 10 mL of water and 50 mL of ether and the organic layer was washed with an additional 10 mL of water. The combined aqueous layers were acidified with concentrated HCl and extracted with four 100-mL portions of ethyl acetate. The combined organic layers were washed with 50 mL of brine, dried ($MgSO_4$) and concentrated in vacuo to afford 2.16 g

of a white solid (mp 155-156.5°C). Recrystallization from ethyl acetate/hexanes gave 1.92 g (87%) of pure, crystalline acid: mp 158-159°C; IR ($CHCl_3$) 2300-3500 (max at 2960), 1720, 1630, 1590, 1482, 1460, 1445, 1411, 1349, 1331, 1295, 1172, 1160, 1100, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.57 (s, 1, NC<u>H</u>S), 3.67 (m, 1, NC<u>H</u>$_2$), 3.33 (m, 1, NC<u>H</u>$_2$), 2.94 (quintet, 1, J = 6.8 Hz, SC<u>H</u>CH_3), 2.49 (m, 2, O=CC<u>H</u>$_2$), 1.79 (m, 4, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.30 (two overlapping d, 6, J = 6.8 Hz, $SCH(C\underline{H}_3)_2$).

<u>Anal.</u> calcd. for $C_{10}H_{17}NO_3S$: C, 51.92; H, 7.41; N, 6.06. Found: C, 52.22; H, 7.36; N, 6.35.

<u>2,4-Dimethoxy-3-methylphenyl α-(2-Propylthio)-2-oxo-1-piperidineacetate (63a)</u>. To a stirred solution of 0.806 g (3.49 mmol) of valerolactam (<u>64</u>), 0.672 g (4.00 mmol) of phenol <u>19a</u>, and 0.104 g (0.085 mmol) of 4-dimethylaminopyridine in 7 mL of dichloromethane protected with a $CaSO_4$ drying tube was added 0.790 g (3.84 mmol) of <u>N</u>,<u>N</u>'-dicyclohexylcarbodiimide in 3 mL of dichloromethane. After 24 h at room temperature, the precipitated <u>N</u>,<u>N</u>'-dicyclohexylurea was removed via filtration and the filtrate was concentrated in vacuo. The residue was dissolved in toluene, filtered to remove additional precipitate, and evaporated at reduced pressure. Purification by MPLC (LoBar size B column, 35:65 ethyl

acetate:hexanes) afforded 1.19 g (89%) of a pale yellow oil: IR ($CHCl_3$) 2950, 1760, 1640, 1484, 1461, 1439, 1418, 1350, 1293, 1240, 1153, 1108 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.87 (s, 1, NC<u>H</u>S), 6.84 (d, 1, J = 9 Hz, aromatic-<u>H</u>), 6.52 (d, 1, J = 9 Hz, aromatic-<u>H</u>), 3.3-3.9 (m, 8, $NC\underline{H}_2$ and two $OC\underline{H}_3$ singlets at δ 3.77 and δ 3.71), 3.03 (quintet, 1, J = 6.8 Hz, $SC\underline{H}CH_3$), 2.43 (m, 2, $O=CC\underline{H}_2$), 2.11 (s, 3, aromatic-$C\underline{H}_3$), 1.81 (m, 4, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.36 (two overlapping d, 6, J = 6.8 Hz, $SCH(C\underline{H}_3)_2$).

2,4-Dimethoxy-3-methylphenyl <u>E</u>-2-propenoate (68).

To a stirred solution of 5.30 g (31.5 mmol) of phenol 19a, 3.25 g (37.8 mmol) of <u>E</u>-2-propenoic acid and 0.38 g (3.11 mmol) of 4-dimethylaminopyridine in 75 mL of dichloromethane protected with $CaSO_4$ drying tube at 0°C was added 8.00 g (39.0 mmol) of <u>N</u>,<u>N</u>'-dicyclohexylcarbodiimide in 25 mL of dichloromethane. After 15 min at 0°C, the reaction mixture was allowed to warm to room temperature for 8 h. The precipitated <u>N</u>,<u>N</u>'-dicyclohexylurea was removed by filtration and the filtrate was concentrated in vacuo, dissolved in hexanes, and refiltered to remove additional precipitate. The crude material obtained upon evaporation of the filtrate

was purified by flash chromatography on 200 g of silica gel (25:75 ethyl acetate:hexanes) to afford 6.81 g (91%) of a white solid (mp 52-55°C). An analytical sample was prepared by recrystallization from hexanes to give colorless needles: mp 55.5-57°C; IR ($CHCl_3$) 3000, 2940, 2830, 1733, 1650, 1595, 1480, 1460, 1435, 1406, 1305, 1235, 1160, 1150, 1110, 1095, 1012, 990, 965, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16 (d of q, 1, J_d = 15.5 Hz, J_q = 7 Hz, =C<u>H</u>CH_3), 6.84 (d, 1, J = 9 Hz, aromatic-<u>H</u>), 6.54 (d, 1, J = 9 Hz, aromatic-<u>H</u>), 6.03 (d of q, 1, J_d = 15.5 Hz, J_q = 1.5 Hz, =C<u>H</u>C=O), 3.77 (s, 3, OC<u>H</u>$_3$), 3.70 (s, 3, OC<u>H</u>$_3$), 2.14 (s, 3, aromatic-C<u>H</u>$_3$), 1.93 (d of d, 3, J = 7 and 1.5 Hz, =CHC<u>H</u>$_3$).

<u>Anal.</u> calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.17; H, 6.63.

<u>2,4-Dimethoxy-3-methylphenyl α-Hydroxy-2-oxo-1-piperidineacetate (63d)</u>. A stirred solution of 1.0 g (4.20 mmol) of crotonate <u>68</u> in 40 mL of 1:1 dichloromethane:methanol protected with a $CaSO_4$ drying tube and cooled to -78°C was bubbled with a stream of ozone in oxygen until the solution turned blue. The excess ozone was removed by bubbling with nitrogen, and 8 mL of dimethyl sulfide was added. The solution was allowed to warm to room temperature and stir for 2.5 h, followed by

concentration in vacuo to afford 1.38 g of a thick oil containing the glyoxalate-methanol adduct 69 and dimethyl sulfoxide. (See the procedure for the preparation of 77a for information concerning the purification and spectral characterization of 69.)

A solution of the crude glyoxalate 69 and 306 mg (3.08 mmol) of valerolactam (64) in 16 mL of dichloromethane was allowed to stand over 4Å sieves for 15 h. After removal of the sieves by filtration, the filtrate was evaporated at reduced pressure to afford a thick oil. Flash chromatography on 70 g of silica gel (ethyl acetate) gave 692 mg (70%) of a white solid: mp 89-91°C; IR ($CHCl_3$) 3540, 3000, 2950, 1765, 1640, 1600, 1483, 1462, 1415, 1302, 1242, 1175, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.89 (d, 1, J = 9 Hz, aromatic-H), 6.54 (d, 1, J = 9 Hz, aromatic-H), 5.81 (br s, 1, OCH), 4.68 (br, 1, OH), 3.79 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 3.52 (m, 2, NCH_2), 2.46 (m, 2, $O{=}CCH_2$), 2.14 (s, 3, aromatic-CH_3), 1.84 (m, 4, $CH_2CH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$) δ 171.2, 168.4, 156.3, 150.0, 137.1, 120.9, 119.5, 105.5, 76.9, 60.7, 55.6, 44.8, 32.0, 22.7, 20.6, 8.9.

Anal. calcd. for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.40; H, 6.49; N, 4.26.

2,4-Dimethoxy-3-methylphenyl α-Acetyloxy-2-oxo-1-

piperidineacetate (63c). A stirred solution of 2.66 g (11.27 mmol) of crotonate 68 in 300 mL of methanol protected with a $CaSO_4$ drying tube and cooled to -78°C was bubbled with a stream of ozone in oxygen for 20 min until the solution turned blue. The excess ozone was removed by bubbling with argon, 20 mL of dimethyl sulfide was added, and the solution was allowed to warm to 0°C for 1 h followed by room temperature for 5.5 h. The solvents were evaporated in vacuo and the residue was dissolved in dichloromethane, dried ($MgSO_4$) and concentrated in vacuo to afford a thick, colorless oil containing the glyoxalate-methanol adduct 69 and dimethyl sulfoxide. (See the procedure for the preparation of 77a for information concerning the purification and spectral characterization of 69.)

A solution of the crude 69 in 8 mL of dichloromethane was added to a solution of 0.838 g (8.54 mmol) of valerolactam (64) in 25 mL of dichloromethane over 4Å sieves. After standing for 14 h at room temperature, the sieves were removed by filtration and the filtrate was concentrated in vacuo to afford a thick yellow oil containing crude 63d.

To a solution of the crude 63d in 7 mL of dichloromethane protected with a $CaSO_4$ drying tube at 0°C was

added 6 mL of acetic anhydride and 12 mL of pyridine. After stirring for 15 min at 0°C followed by 1 h at room temperature, the reaction mixture was partitioned between 400 mL of ether and 100 mL of ice cold 1 M aqueous HCl. The organic layer was washed with 100 mL of ice cold 1 M aqueous HCl, two 75-mL portions of saturated aqueous $NaHCO_3$, and 50 mL of brine, dried ($MgSO_4$) and concentrated in vacuo to give 4.1 g of a thick, orange oil. The crude product was purified by MPLC (LoBar size C column), collecting 20 mL fractions and eluting with hexanes (fractions 1-5), 60:40 ethyl acetate:hexanes (fractions 6-73) and 75:25 ethyl acetate:hexanes (fractions 74-100). Fractions 49-74 afforded 2.39 g (77%, overall from 64) of a pale yellow solid (mp 81.5-83.5°C). An analytical sample was prepared by recrystallization from benzene/hexanes to afford white crystals: mp 84.5-85°C; IR ($CHCl_3$) 3020, 2970, 2850, 1780, 1755, 1670, 1660, 1608, 1490, 1468, 1445, 1420, 1378, 1354, 1298, 1290, 1248, 1175, 1115, 1046, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (s, 1, OC$\underline{H}$), 6.93 (d, 1, J = 9 Hz, aromatic-$\underline{H}$), 6.58 (d, 1, J = 9 Hz, aromatic-$\underline{H}$), 3.78 (s, 3, OC$\underline{H}_3$), 3.72 (s, 3, OC$\underline{H}_3$), 3.52 (m, 2, NC$\underline{H}_2$), 2.50 (m, 2, O=CC$\underline{H}_2$), 2.17 (s, 3, CC$\underline{H}_3$), 2.13 (s, 3, CC$\underline{H}_3$), 1.84 (m, 4, $CH_2C\underline{H}_2C\underline{H}_2CH_2$).

Anal. calcd. for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.35; N, 3.83. Found: C, 58.99; H, 6.35; N, 3.73.

Mercury(II) Trifluoromethanesulfonate[58] (70). To a suspension of 4.3 g (20 mmol) of red mercury(II) oxide in 50 mL of benzene at room temperature under argon was added 5 mL (30 mmol) of trifluoromethanesulfonic anhydride. The stirred suspension was heated to reflux for 5 h at which point nearly all of the red solid had dissolved and a white solid had precipitated. After cooling to room temperature for 1 h, the solid was collected on a glass frit washed with several portions of benzene (50 mL total) and dissolved in 35 mL of acetonitrile. The solution was filtered to remove a small amount of insoluble residue, and benzene (55 mL) was added to the filtrate to induce crystallization. After cooling to 0°C, the white needles were collected, washed with benzene and dried under vacuum at 110°C to afford 5.46 g (55%) of pure, solvent-free mercury(II) trifluoromethanesulfonate: mp >300°C (dec).

Anal. calcd. for $C_2F_6HgO_6S_2$: C, 4.82; S, 12.86; Hg, 40.22. Found: C, 4.93; S, 12.76; Hg, 39.78.

In a separate experiment, the mercury(II) trifluoromethanesulfonate thus obtained was dried under vacuum at room temperature instead of 110°C. Integration

of the ^{1}H NMR spectra (DMSO-d_6) employing chloroform as a quantitative internal standard revealed that this material was an acetonitrile solvate possessing the following stoichiometry: $Hg(OSO_2CF_3)_2 \cdot (CH_3CN)_{1.74}$.

1-[5,7-Dimethoxy-6-methyl-2-oxo-3(2H)-benzofuranyl]-2-piperidone (62). (a) Via the Reaction of Sulfide 63a With Mercury(II) Trifluoromethanesulfonate. To a stirred solution of 468 mg (1.23 mmol) of sulfide 63a in 7 mL of dichloromethane at room temperature under argon was added 679 mg (1.35 mmol) of mercury(II) trifluoromethanesulfonate to afford a white suspension. After 45 min, the suspension was diluted with dichloromethane and filtered to remove the suspended solid. The filtrate was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to yield 384 mg of a yellow oil. The crude material was purified by MPLC (LoBar size B column, 70:30 followed by 80:20 ethyl acetate:hexanes) to afford 300 mg (80%) of a white solid (mp 142.5-144°C). An analytical sample was prepared by recrystallization from benzene/hexanes to provide white needles: mp 143-144°C; IR ($CHCl_3$) 3020, 2965, 1812, 1648, 1612, 1467, 1425, 1350, 1295, 1225, 1140, 1094, 1078, 1065, 1018, 978 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 6.42 (s, 1, aromatic-H), 6.09 (br s, 1, NCH), 3.98

(s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.22 (m, 2, NCH_2), 2.49 (m, 2, $O{=}CCH_2$), 2.07 (s, 3, aromatic-CH_3), 1.83 (m, 4, $CH_2CH_2CH_2CH_2$); ^{13}C NMR (CH_2Cl_2) δ 172.5, 170.3, 155.8, 143.0, 139.3, 122.2, 120.7, 100.7, 60.7, 57.4, 56.6, 47.8 (br), 32.6, 23.6, 21.6, 9.2.

Anal. calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.94; H, 6.32; N, 4.56.

Exact mass calcd. for $C_{16}H_{19}NO_5$: 305.126. Found: 305.126.

(b) Via the Reaction of Sulfide 63a With Copper(I) Trifluoromethanesulfonate-benzene Complex [$(CuOSO_2CF_3)_2 \cdot C_6H_6$].[56] To a stirred suspension of 874 mg (1.75 mmol) of $(CuOSO_2CF_3)_2 \cdot C_6H_6$ in 6 mL of benzene under argon was added 207.7 mg (0.545 mmol) of sulfide 63a in 3 mL of benzene. After 3.5 h at room temperature, TLC (75:25 ethyl acetate:hexanes) revealed that no reaction had occurred and thus the suspension was heated to 70-75°C for 1 h to afford a yellow solution. After cooling to room temperature, the reaction mixture was stirred with 10 mL of water and the precipitate which formed was removed by filtration. The filtrate was partitioned between ether and 1 M aqueous HCl, and some additional precipitate was removed by filtration. The organic layer was washed with brine, dried ($MgSO_4$)

and concentrated in vacuo to afford 188 mg of a brown oil. Purification by MPLC (LoBar size A column, 45:55 ethyl acetate:hexanes) gave 99.2 mg (60%) of lactone 62 as an off-white solid.

(c) Via the Reaction of Chloride 63b With Silver(I) Trifluoromethanesulfonate.[59] To a stirred solution of 202.1 mg (0.625 mmol) of alcohol 63d in 5 mL of dichloromethane under argon was added 60 µl (0.822 mmol) of thionyl chloride over 1 min. After 2.5 h at room temperature, the solution was concentrated in vacuo to afford 223 mg (104%) of chloride 63b as a yellow oil: IR (CH_2Cl_2) 3060, 2965, 1778, 1670, 1486, 1460, 1415, 1285, 1242, 1160, 1110, 1012, 983, 895, 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (s, 1, ClC<u>H</u>), 6.85 (d, 1, J = 9 Hz, aromatic-<u>H</u>), 6.52 (d, 1, J = 9 Hz, aromatic-<u>H</u>), 3.76 (s, 3, OC<u>H</u>$_3$), 3.68 (s, 3, OC<u>H</u>$_3$), 3.58 (m, 2, NC<u>H</u>$_2$), 2.49 (m, 2, O=CC<u>H</u>$_2$), 2.13 (s, 3, aromatic-C<u>H</u>$_3$), 1.86 (m, 4, $CH_2C\underline{H}_2C\underline{H}_2CH_2$).

A solution of the crude chloride 63b in 4 mL of dichloromethane was added dropwise over 12 min to a rapidly stirred suspension of 191 mg (0.743 mmol) of silver(I) trifluoromethanesulfonate in 4 mL of dichloro-

methane under argon. After 45 min at room temperature, 5 mL of dichloromethane and 2 mL of 1:1 2 M aqueous Na_2CO_3:brine was added. The suspension which resulted was stirred rapidly for 5 min, the precipitated silver chloride was removed by filtration through celite and the filter pad was washed with dichloromethane. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield 209 mg of a yellow oil. The crude product was purified by MPLC (LoBar size B column, equilibrated with 40:60 ethyl acetate:hexanes, eluted with 70:30 ethyl acetate:hexanes followed by neat ethyl acetate) to afford 152.4 mg (80%, overall from 63d) of lactone 62 as a white solid.

(d) Via the Reaction of Chloride 63b With Tin Tetrachloride. Chloride 63b was prepared as described in part (c) from 98 mg (0.303 mmol) of alcohol 63d and 0.036 mL (0.490 mmol) of thionyl chloride. To a stirred solution of the crude chloride in 3 mL of dichloromethane at 0°C under argon was added 0.35 mL (0.35 mmol) of 1 M tin tetrachloride in dichloromethane over 2 min. After stirring for 1 h at 0°C followed by 3.5 h at room temperature, the solution was partitioned between dichloromethane and 1:1 2 M aqueous Na_2CO_3:brine. The organic layer was dried (Na_2SO_4) and concentrated in

vacuo to yield 81 mg of a pale yellow oil. Flash chromatography on 8 g of silica gel (equilibrated with 50:50 ethyl acetate:hexanes, eluted with neat ethyl acetate) afforded 60.7 mg (66%) of lactone 62 as a white solid.

(e) Via the Reaction of Acetate 63c With Boron Trifluoride Etherate. To a stirred solution of 429 mg (1.17 mmol) of acetate 63c in 7 mL of benzene under argon was added 0.29 mL (2.35 mmol) of boron trifluoride etherate. After 0.5 h at room temperature, heating to 60°C for 6 h afforded a brown solution with suspended solids. The reaction mixture was partitioned between 50 mL of dichloromethane and 10 mL of saturated aqueous $NaHCO_3$, and the aqueous phase was re-extracted with 50 mL of dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to yield 400 mg of a foam. The crude product was purified by MPLC (LoBar size B column, equilibrated with hexanes, eluted with 70:30 ethyl acetate:hexanes followed by 80:20 ethyl acetate:hexanes) to afford 208 mg (58%) of lactone 62 as an off-white solid.

Reaction of Sulfide 63a With $Hg(OSO_2CF_3)_2 \cdot (CH_3CN)_{1.74}$. To a stirred solution of 163.2 mg (0.43 mmol) of sulfide 63a in 4 mL of dichloromethane under argon was added

284.0 mg (0.50 mmol) of $Hg(OSO_2CF_3)_2 \cdot (CH_3CN)_{1.74}$. After 0.5 h at room temperature, the reaction was quenched with 5 M aqueous NaOAc and allowed to stir 5 min. The mixture was partitioned between dichloromethane and 5 M aqueous NaOAc and the organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford an oil. TLC (ethyl acetate) and ^1H NMR revealed that in addition to lactone 62, another more polar substance had formed. These products were separated by MPLC (LoBar size A column), eluting with ethyl acetate and collecting 4 mL fractions. Fractions 5-7 gave 54.3 mg (41%) of lactone 62 and fractions 18-33 gave 46.0 mg (30%) of acetamide 63g as a colorless oil.

63g: IR ($CHCl_3$) 2900-3600 (sharp band at 3430), 3000, 2960, 1765, 1675, 1635, 1600, 1480, 1300, 1240, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.49 (d, 1, J = 8.5 Hz, NH), 6.92 (d, 1, J = 9 Hz, aromatic-H), 6.57 (d, 1, J = 9 Hz, aromatic-H), 5.71 (d, 1, J = 8.5 Hz, NCH), 3.5-4.0 (m, 8, NCH_2 and two OCH_3 singlets at δ 3.79 and δ 3.70), 2.39 (m, 2, $O{=}CCH_2$), 2.11 (s, 3, CCH_3), 2.04 (s, 3, CCH_3), 1.83 (m, 4, $CH_2CH_2CH_2CH_2$).

Exact mass calcd. for $C_{18}H_{24}N_2O_6$: 364.164. Found: 364.163.

Ethyl α-Chloro-2-oxo-1-piperidineacetate (72). To a

stirred solution of 716.3 mg (3.56 mmol) of alcohol 65 in 20 mL of dichloromethane protected with a $CaSO_4$ drying tube was added 0.4 mL (5.50 mmol) of thionyl chloride. After 1.5 h at room temperature, the solvent was evaporated in vacuo to afford 778.1 mg (99%) of a pale yellow oil: IR (neat) 2970, 1762, 1680, 1485, 1468, 1415, 1350, 1300, 1190, 1092, 1025, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.93 (s, 1, ClC<u>H</u>), 4.24 (q, 2, J = 7 Hz, OC<u>H</u>$_2$), 3.44 (m, 2, NC<u>H</u>$_2$), 2.47 (m, 2, O=CC<u>H</u>$_2$), 1.87 (m, 4, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.31 (t, 3, J = 7 Hz, C<u>H</u>$_3$).

<u>Exact mass</u> calcd. for $C_9H_{14}{}^{35}ClNO_3$: 219.066. Found: 219.066.

<u>Ethyl α-(2,5-Dimethoxyphenyl)-2-oxo-1-piperidine-acetate (73)</u>. To a stirred solution of 138.1 mg (0.63 mmol) of chloride 72 and 130.5 mg (0.95 mmol) of 1,4-dimethoxybenzene in 4 mL of dichloromethane under argon was added 90 µL (0.76 mmol) of tin tetrachloride. After 1 h at room temperature, the reaction mixture was diluted with 10 mL of dichloromethane and quenched with 3 mL of 2 M aqueous Na_2CO_3. The resulting suspension was rapidly stirred for 10 min and subsequently filtered through celite. The aqueous layer was diluted with 3 mL of brine and re-extracted with two 10-mL portions of dichloromethane. The combined organic layers were

dried (Na_2SO_4) and concentrated in vacuo to yield 225 mg of a pale yellow oil. Flash chromatography on 18 g of silica gel (packed in ethyl acetate, eluted with 98:2 ethyl acetate:methanol) afforded 174.9 mg (86%) of a white solid (mp 87-89°C). An analytical sample was prepared by recrystallization from ether/hexanes to give pure 73 as colorless crystals: mp 89-90.5°C; IR ($CHCl_3$) 3010, 2960, 2840, 1740, 1630, 1500, 1463, 1435, 1417, 1370, 1350, 1330, 1295, 1230, 1168, 1045, 1027, 810, 650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.81 (s, 2, aromatic-H), 6.74 (s, 1, aromatic-H), 6.41 (s, 1, NCH), 4.17 (q, 2, J = 7.3 Hz, OCH_2), 3.73 (s, 6, OCH_3), 3.43 (m, 1, NCH_2), 2.80 (m, 1, NCH_2), 2.44 (m, 2, $O{=}CCH_2$), 1.74 (m, 4, $CH_2CH_2CH_2CH_2$), 1.23 (t, 3, J = 7.3 Hz, CH_2CH_3).

Anal. calcd. for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.49; H, 7.18; N, 4.33.

1,3-Dimethoxy-2-methyl-4-(trimethylsilyl)oxybenzene (19b) was prepared by the reaction of phenol 19a with diethyltrimethylsilylamine in dichloromethane at room temperature. Bulb-to-bulb distillation (115°C, 0.05 mm) of the crude product afforded silyl ether 19b as a pale yellow liquid: IR (CH_2Cl_2) 3060, 2970, 2850, 1595, 1490, 1470, 1445, 1420, 1270, 1251, 1223, 1163,

1112, 1038, 998, 880, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.61 (d, 1, J = 9 Hz, aromatic-H), 6.41 (d, 1, J = 9 Hz, aromatic-H), 3.72 (s, 6, OCH_3), 2.12 (s, 3, aromatic-CH_3), 0.23 (s, 9, $SiCH_3$).

Exact mass calcd. for $C_{12}H_{20}O_3Si$: 240.1182. Found: 240.1178.

Purification and Characterization of Intermolecular Amidoalkylation Products 59a, 60a, 60b and 74: Reaction of Chloride 72 With Silyl Ether 19b and Tin Tetrachloride. To a stirred solution of 208.3 mg (0.85 mmol) of silyl ether 19b in 4 mL of dichloromethane at 0 C under argon was added 0.85 mL (0.85 mmol) of 1 M tin tetrachloride in dichloromethane over 2 min to afford a yellow suspension. After 8 min at 0°C, a solution of 149.2 mg (0.68 mmol) of chloride 72 in 3 mL of dichloromethane was added. The reaction mixture was maintained at 0°C for 50 min during which the yellow precipitate dissolved, quenched with 5 mL of 1:1 2 M aqueous Na_2CO_3:brine and diluted with 10 mL of dichloromethane. The resulting suspension was rapidly stirred for 5 min at room temperature and subsequently extracted with dichloromethane. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford 288 mg of a pale yellow oil. ^1H NMR and TLC (ethyl acetate, 25:75 acetone:dichloromethane)

revealed that several products were present, and that no lactone 62 had formed. The coproducts were separated by MPLC on a LoBar size B column, equilibrated with 33:67 ethyl acetate:hexanes and eluted with 60:40 ethyl acetate:hexanes (fractions 1-30) followed by 75:25 ethyl acetate:hexanes (fractions 31-70). Approximately 20-mL fractions were collected. Fractions 19-22 afforded 25.3 mg (8.5%) of phenyl ether 74 as a colorless oil. An analytical sample of 74 was prepared by bulb-to-bulb distillation at 90°C (0.015 mm). Fractions 33-38 afforded 26.3 mg (8.8%) of silyl ether 60b as a colorless oil. The regiochemical assignment of the above silyl ether was based on its clean conversion to phenol 60a upon treatment with triethylamine in methanol at room temperature. Fractions 43-46 afforded 46.1 mg (15.4%) of phenol 59a as a white solid. An analytical sample of 59a was prepared by recrystallization from benzene/hexanes followed by dichloromethane/hexanes. Fractions 47-48 afforded 31 mg (10.4%) of a mixture of 59a and 60a (59a:60a = 1.2:1). Fractions 49-90 gave 90.5 mg (30.3%) of phenol 60a contaminated with approximately 10% of 59a. Recrystallization of the impure material from benzene/hexanes yielded an analytically and spectroscopically pure sample of 60a

as a white solid.

74: IR ($CHCl_3$) 3020, 2960, 1750, 1650, 1600, 1485, 1462, 1440, 1415, 1350, 1330, 1297, 1230, 1110, 1018 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (d, 1, J = 9 Hz, aromatic-H), 6.78 (s, 1, NCH), 6.46 (d, 1, J = 9 Hz, aromatic-H), 4.28 (q, 2, J = 7.5 Hz, OCH_2), 3.83 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.0-3.8 (m, 2, NCH_2), 2.39 (m, 2, $O{=}CCH_2$), 2.12 (s, 3, aromatic-CH_3), 1.76 (m, 4, $CH_2CH_2CH_2CH_2$), 1.31 (t, 3, J = 7.5 Hz, CH_2CH_3).

Anal. calcd. for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.85; H, 7.31; N, 3.49.

59a: mp 150.5-151.5°C; IR ($CHCl_3$) 3540, 3020, 2960, 1740, 1628, 1490, 1465, 1420, 1210, 1130, 1025, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.49 (br, 1, OH), 6.39 (s, 2, aromatic-H and NCH), 4.22 (q, 2, J = 7.3 Hz, OCH_2), 3.77 (s, 3, OCH_3), 3.72 (s, 3, OCH_3), 3.53 (m, 1, NCH_2), 2.95 (m, 1, NCH_2), 2.47 (m, 2, $O{=}CCH_2$), 2.15 (s, 3, aromatic-CH_3), 1.77 (m, 4, $CH_2CH_2CH_2CH_2$), 1. 26 (t, 3, J = 7.3 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 171.1 (s), 170.3 (s), 151.2 (s), 146.6 (s), 142.5 (s), 121.1 (s), 117.5 (s), 107.9 (d), 61.4 (t), 60.8, 56.5, 56.1, 44.6 (t), 32.3 (t), 23.1 (t), 20.9 (t), 14.2 (q), 9.4 (q).

Anal. calcd. for $C_{18}H_{25}N_2O_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.59; H, 7.09; N, 3.90.

60a: mp 154-156°C; IR ($CHCl_3$) 3545, 3020, 2960, 1738, 1630, 1497, 1453, 1450, 1420, 1350, 1332, 1300, 1190, 1115, 1050, 1025, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.62 (s, 1, aromatic-H or NCH), 6.49 (s, 1, aromatic-H or NCH), 6.21 (s, 1, OH), 4.20 (q, 2, J = 7.5 Hz, OCH_2), 3.79 (s, 3, OCH_3), 3.65 (s, 3, OCH_3), 3.38 (m, 1, NCH_2), 2.85 (m, 1, NCH_2), 2.47 (m, 2, $O{=}CCH_2$), 2.25 (s, 3, aromatic-CH_3), 1.75 (m, 4, $CH_2CH_2CH_2CH_2$), 1.25 (t, 3, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) δ 171.0 (s), 170.7 (s), 151.0 (s), 146.7 (s), 145.6 (s), 125.0 (s), 122.8 (s), 114.2 (d), 61.3, 61.0, 60.5, 55.6, 45.0 (t), 32.4 (t), 23.2, 20.9, 14.1 (q), 10.1 (q).

Anal. calcd. for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.36; H, 7.03; N, 3.82.

Ethyl α-(2-Hydroxy-3,5-dimethoxy-4-methylphenyl)-2-oxo-1-piperidineacetate (59a) Via Ethanolysis of Lactone 62. A solution of 43.3 mg (0.14 mmol) of lactone 62 in 4 mL of absolute ethanol containing two drops of triethylamine was allowed to stir for 12 h at room temperature. Concentration in vacuo afforded a pale yellow oil which was identical by ^1H NMR and TLC (ethyl acetate) to the less polar regioisomer obtained in the intermolecular amidoalkylation reaction.

Lewis Acid Promoted Amidoalkylation Reactions of

Chloride 72 With Phenol Derivatives 19a and 19b (Table 2). Determination of the Regioisomer Ratio. The reactions listed in Table 2 were carried out according to the experimental procedures described below. Phenols 59a and 60a were isolated together from the crude product by flash chromatography. The ratio of 59a:60a was determined by integration of the ^{1}H NMR spectrum of the mixture of 59a and 60a thus obtained. Two sets of signals were employed for integration: the benzylic methyl protons and the sum of the aromatic proton and benzylic methine proton. The latter set of signals were integrated after D_2O exchange of the overlapping phenol hydroxyl proton. The values for 59a:60a reported in Table 2 are an average of the values obtained by these two methods. The crude reaction products derived from silyl ether 19b (Entries G-J) were treated with triethylamine in absolute methanol at room temperature to convert all silyl ether by-products to the corresponding phenols prior to chromatography and isomer ratio determination.

Table 2, Entry A. To a stirred solution of 116 mg (0.69 mmol) of phenol 19b in 3 mL of dichloromethane at 0°C under argon was added 0.72 mL (0.72 mmol) of 1 M tin tetrachloride in dichloromethane over 2 min. The

yellow solution was allowed to warm to room temperature for 1 h. After cooling to 0°C, a solution of 111.1 mg (0.506 mmol) of chloride 72 in 3 mL of dichloromethane was added. The reaction mixture was allowed to stir at 0°C for 1 h, when it was diluted with 20 mL of dichloromethane, quenched with 6 mL of 1:1 2 M aqueous Na_2CO_3:brine and stirred rapidly for 10 min. The aqueous layer was separated and washed with an additional 15 mL of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 203 mg of a pale yellow oil. Flash chromatography on 18 g of silica gel (ethyl acetate) gave 140 mg (79%) of a mixture of 59a and 60a in a 2.5:1 ratio.

Table 2, Entry B. To a stirred solution of 164.5 mg (0.749 mmol) of chloride 72 and 149 mg (0.89 mmol) of phenol 19a in 8 mL of dichloromethane at -78°C under argon was added 0.92 mL (0.92 mmol) of 1 M tin tetrachloride in dichloromethane. The yellow solution was maintained at -78°C for 1.5 h, warmed to between -50°C and -40°C for 1 h, warmed to 0°C gradually over 0.5 h, and finally maintained at 0°C for 0.5 h. TLC (ethyl acetate) indicated that the reaction did not proceed at a significant rate until -20°C was reached. The reaction mixture was diluted with dichloromethane,

quenched with 6 mL of 1:1 2 M aqueous Na_2CO_3:brine and stirred rapidly for 10 min. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo to afford 286 mg of a pale yellow oil. Flash chromatography on 20 g of silica gel (ethyl acetate) gave 218.6 mg (83%) of a mixture of 59a and 60a in a 2.6:1 ratio.

Table 2, Entry C. To a stirred solution of 89 mg (0.53 mmol) of phenol 19a and 102.8 mg (0.47 mmol) of chloride 72 in 5 mL of dichloromethane at 0°C under argon was added 65 µl (0.53 mmol) of boron trifluoride etherate. After 1 h at 0°C, the reaction mixture was allowed to warm to room temperature for 18 h, diluted with dichloromethane, quenched with 5 mL of 1:1 2 M aqueous Na_2CO_3:brine and stirred rapidly for 10 min. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford 181 mg of a yellow oil. Flash chromatography on 20 g of silica gel (ethyl acetate) gave 137.1 mg (83%) of a mixture of 59a and 60a in a 1.8:1 ratio.

Table 2, Entry D. To a stirred solution of 112.5 mg (0.512 mmol) of chloride 72 and 95.5 mg (0.57 mmol) of phenol 19a in 5 mL of dichloromethane at 0°C under argon was added 70 µl (0.64 mmol) of titanium tetrachloride. After 1 h at 0°C, the reaction mixture was

allowed to warm to room temperature for 18 h, diluted with dichloromethane quenched with 5 mL of 1:1 2 M aqueous Na_2CO_3:brine, and stirred rapidly for 10 min. The suspension was filtered through celite to remove insoluble salts, and the aqueous layer was separated and extracted with additional dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 200 mg of a pale yellow oil. ^1H NMR and TLC (ethyl acetate) indicated that much starting materials (19a and 73) remained. Flash chromatography on 20 g of silica gel (ethyl acetate) gave 44.2 mg (25%) of a mixture of 59a and 60a in a 0.17:1 ratio.

Table 2, Entry E. To a stirred suspension of 160 mg (0.62 mmol) of silver(I) trifluoromethanesulfonate and 108 mg (0.64 mmol) of phenol 19a in 5 mL of dichloromethane at 0°C under argon was added 111.2 mg (0.506 mmol) of chloride 72 in 2 mL of dichloromethane. After 1 h at 0°C, the reaction mixture was quenched with 2 mL of brine and rapidly stirred for 10 min. Additional dichloromethane and 2 mL of 2 M aqueous Na_2CO_3 were added and the insoluble silver salts were removed by filtration through celite. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to

afford 201 mg of an oil. Flash chromatography on 18 g of silica gel (75:25 ethyl acetate:hexanes followed by neat ethyl acetate) gave 100.9 mg (57%) of aryl ether 74 as a colorless oil followed by 50.7 mg (29%) of a mixture of 59a and 60a in a 2.7:1 ratio.

Table 2, Entry F. To a stirred solution of 60.5 mg (0.36 mmol) of phenol 19a and 80 µl (0.68 mmol) of tin tetrachloride in 2.5 mL of dichloromethane at -78°C under argon was added 60 µl (0.34 mmol) of ethyldiisopropylamine to afford an orange, crystalline precipitate. After 5 min at -78°C, a solution of 67.3 mg (0.307 mmol) of chloride 72 in 3 mL of dichloromethane was added causing dissolution of the precipitate to give a yellow-orange solution. The solution was allowed to stir for 5 min at -78°C, warmed to 0°C for 1 h, diluted with dichloromethane and quenched with 4 mL of 1:1 2 M aqueous Na_2CO_3:brine. The aqueous layer was re-extracted with 10 mL of dichloromethane and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 126 mg of an oil. Flash chromatography on 12 g of silica gel (60:40 ethyl acetate:hexanes followed by neat ethyl acetate) gave 49.5 mg (46%) of aryl ether 74 followed by 40.3 mg (37%) of a mixture of 59a and 60a in a 7.5:1 ratio.

Table 2, Entry G. To a stirred solution of 119 mg (0.50 mmol) of silyl ether 19b and 93.4 mg (0.425 mmol) of chloride 72 in 6 mL of dichloromethane at 0°C under argon was added 0.55 mL (0.55 mmol) of 1 M tin tetrachloride in dichloromethane over 2 min. After 1 h at 0°C, the solution was diluted with dichloromethane, quenched with 6 mL of 1:1 2 M aqueous Na_2CO_3:brine and stirred rapidly for 10 min. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to afford 169 mg of a yellow oil. Desilylation (2 drops Et_3N, 3 mL CH_3OH, 3 h) followed by flash chromatography on 20 g of silica gel (ethyl acetate) afforded 122.5 mg (82%) of a mixture of 59a and 60a in a 0.76:1 ratio.

Table 2, Entry H. To a stirred solution of 212 mg (0.88 mmol) of silyl ether 19b in 4 mL of dichloromethane at 0°C under argon was added 0.92 mL (0.92 mmol) of 1 M tin tetrachloride in dichloromethane over 3 min. Upon warming to room temperature for 2 h, a yellow precipitate formed. The stirred suspension was cooled to 0°C and 154.8 mg (0.705 mmol) of chloride 72 in 3 mL of dichloromethane was added. The reaction mixture was maintained at 0°C for 1 h during which the yellow precipitate dissolved. The solution was diluted with dichloromethane, quenched with 6 mL of 1:1 2 M aqueous

Na_2CO_3:brine and stirred rapidly for 10 min. The aqueous layer was separated and extracted with additional dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 292 mg of a pale yellow oil. Desilylation (2 drops Et_3N, 3 mL CH_3OH, 1 h) followed by flash chromatography on 20 g of silica gel (ethyl acetate) gave 201 mg (81%) of a mixture of 59a and 60a in a 0.78:1 ratio.

Table 2, Entry I. To a stirred solution of 120 mg (0.50 mmol) of silyl ether 19b in 3 mL of dichloromethane at room temperature under argon was added 1.1 mL (1.10 mmol) of 1 M tin tetrachloride in dichloromethane over 2 min. A yellow precipitate formed within 10 min, and the suspension was allowed to stir for 6 h at room temperature. After cooling to 0°C, a solution of 98.6 mg (0.448 mmol) of chloride 72 in 3 mL of dichloromethane was added. The reaction mixture was maintained at 0°C for 1 h during which the precipitate dissolved. The solution was diluted with dichloromethane, quenched with 6 mL of 1:1 2 M aqueous Na_2CO_3:brine and stirred rapidly for 10 min. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to afford 172 mg of a yellow oil. Desilylation (2 drops

Et_3N, 3 mL CH_3OH, 1 h) followed by flash chromatography on 20 g of silica gel (ethyl acetate) gave 118.3 mg (75%) of a mixture of 59a and 60a in a 2.0:1 ratio.

Table 2, Entry J. To a stirred suspension of 209 mg (0.81 mmol) of silver(I) trifluoromethanesulfonate and 140 mg (0.58 mmol) of silyl ether 19b in 5 mL of dichloromethane at 0°C under argon was added 106.5 mg (0.485 mmol) of chloride 72 in 2 mL of dichloromethane. After 1 h at 0°C, the reaction mixture was quenched with 2 mL of brine and stirred rapidly for 10 min. Following the addition of 2 mL of 2 M aqueous Na_2CO_3, the insoluble salts were removed by filtration through celite and the filter cake was washed with dichloromethane. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to afford 198 mg of a yellow oil. Desilylation (4 drops Et_3N, 4 mL CH_3OH, 2 h) followed by flash chromatography on 20 g of silica gel (70:30 ethyl acetate:hexanes followed by neat ethyl acetate) gave a mixture of 59a and 60a in a 0.23: 1 ratio.

Tin Tetrachloride Promoted Rearrangement of Aryl Ether 74. To a stirred solution of 56.1 mg (0.16 mmol) of aryl ether 74 in 4 mL of dichloromethane at 0°C under argon was added 0.18 mL (0.18 mmol) of 1 M tin tetrachloride in dichloromethane. After 1 h at 0°C,

TLC (ethyl acetate) revealed that the conversion of 74 to 59a and 60a was occurring very slowly. The reaction mixture was allowed to warm to room temperature for 4.5 h, at which point TLC (ethyl acetate) indicated that aryl ether 74 had been consumed. The solution was diluted with dichloromethane, quenched with 4 mL of 1:1 2 M aqueous Na_2CO_3:brine, and rapidly stirred for 5 min. The aqueous layer was separated and extracted with 10 mL of dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated at reduced pressure to afford 56 mg of a pale yellow oil. ^1H NMR and TLC (ethyl acetate) indicated that in addition to the rearranged phenols 59a and 60a, lactone 62 was present as a minor component. In order to convert the lactone 62 into phenol 59a, the crude product was dissolved in 3 mL of absolute ethanol containing three drops of triethylamine. After standing for 1.5 h at room temperature, the solution was concentrated in vacuo. The residue was purified by flash chromatography on 8 g of silica gel (ethyl acetate) to afford 44.4 mg (79%) of a mixture of 59a and 60a in a 4.4:1 ratio, (^1H NMR).

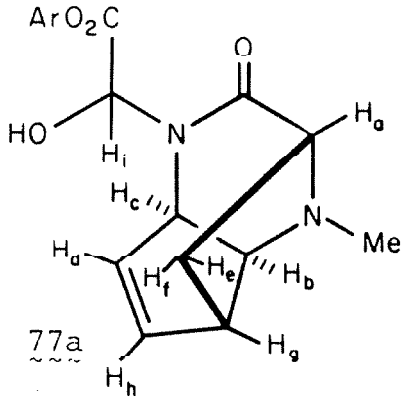
2,4-Dimethoxy-3-methylphenyl [2α,4(S*) and 4(R*),4aβ,7α,7aβ]-1,2,3,4a,7,7a-Hexhydro-α-hydroxy-1-methyl-

3-oxo-2,7-methano-4H-cyclopentapyrazine-4-acetate (77a). A stirred solution of 489 mg (2.07 mmol) of crotonate 68 in 7 mL of methanol and 5 mL of dichloromethane, protected with a $CaSO_4$ drying tube and cooled to -78°C, was bubbled with a stream of ozone in oxygen until the solution turned blue. The excess ozone was removed by bubbling with nitrogen and 3 mL (40.8 mmol) of dimethyl sulfide was added. The reaction mixture was allowed to warm to room temperature and stir for 2 h. The solution was concentrated in vacuo to yield an oil which was purified by flash chromatography on 30 g of silica gel (95:5 dichloromethane:methanol) to afford 552 mg (104%) of phenyl glyoxalate-methanol adduct 69 as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 6.84 (d, 1, J = 9 Hz, aromatic-H), 6.51 (d, 1, J = 9 Hz, aromatic-H), 5.13 (d, 1, J = 11 Hz, OCH), 4.51 (d, 1, J = 11 Hz, OH), 4.74 (s, 3, aromatic-OCH_3), 4.68 (s, 3, aromatic-OCH_3), 3.51 (s, 3, hemiacetal-OCH_3), 2.13 (s, 3, aromatic-CH_3).

A solution of the 552 mg of 69 prepared above and 81.1 mg (0.49 mmol) of 21 in 3.5 mL of dichloromethane was allowed to stand over 4Å sieves at room temperature under argon for 6 h. The reaction mixture was filtered to remove the sieves, and the filtrate was concentrated in vacuo to yield a yellow oil. The crude product was

purified by flash chromatography on 30 g of silica gel (75:25 acetone:dichloromethane) to afford 106.9 mg (56%) of 77a as a mixture of a white solid and a colorless oil. ^{1}H NMR indicated that this material was a 2.2:1 mixture of isomers at position 9.

In a separate experiment, the crude 77a was recrystallized from dichloromethane/hexanes to afford a white solid which was enriched in the major isomer (~4:1 by ^{1}H NMR): mp 112-116°C; IR ($CHCl_3$) 3540, 2960, 1775, 1655, 1660, 1487, 1240, 1165, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.89 (d, 1, J = 9 Hz, aromatic-H), 6.54 (d, 1, J = 9 Hz, aromatic-H), 6.12 (m, 2, H_d, H_h), 5.74 (s, H_i, minor isomer), 5.31 (s, H_i, major isomer), 4.39 (d, 1, J_{cb} = 6 Hz, H_c), 4.20 (br s, 1, OH), 3.93 (t, 1, $J_{bc} = J_{bg}$ = 6 Hz), 3.79 (s, 3, OCH_3), 3.72 (s, 3, OCH_3), 3.55 (m, 1, H_a), 3.07 (m, 1, H_g), 2.62 (s, 3, NCH_3), 2.27 (m, 1, H_e), 2.15 (s, 3, aromatic-CH_3), 1.53 (d of d, 1, J_{fe} = 13.5 Hz, J_{fg} = 3 Hz, H_f).



[2α,4(S*) and 4(R*), 4aβ,7α,7aβ)-1,2,4,4a,7,7a-Hexahydro-4-(5,7-dimethoxy-6-methyl-2-oxo-3(2H)-benzofuranyl)-1-methyl-2,7-methano-3H-cyclopentapyrazin-3-one (78). To a stirred solution of 190 mg (0.49 mmol) of 77a in 5 mL of dichloromethane protected with a $CaSO_4$ drying tube was added 80 µl (1.09 mmol) of thionyl chloride. After 3 h at room temperature, the solution was concentrated in vacuo to afford the hydrochloride salt of 77b as a yellow semi-solid.

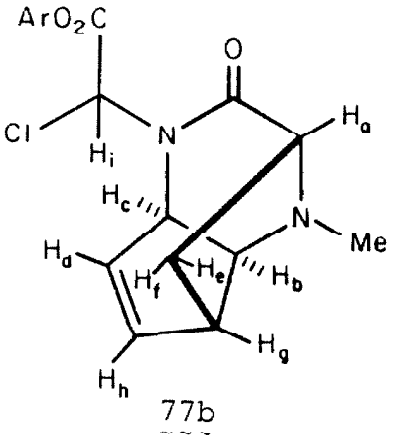
[In a separate experiment, the free amine 77b was isolated via the following procedure: The crude hydrochloride salt was partitioned between dichloromethane and 1:1 2 M aqueous Na_2CO_3:brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. ^1H NMR indicated that this material was an approximately 1:1 mixture of isomers at position 9: ^1H NMR ($CDCl_3$) δ 6.87 (d, 1, J = 9 Hz, aromatic-H), 6.62 and 6.85 (two s, 1, H_i), 6.53 (d, 1, J = 9 Hz, aromatic-H), 5.9-6.4 (m, 2, H_d, H_h), 4.56 (m, 1, H_c), 3.93 (t, 1, $J_{bc} = J_{bg}$ = 6 Hz, H_b), 3.4-3.8 (m, 7, H_a and three OCH_3 singlets at δ 3.68, 3.72 and 3.77) 3.00 (m, 1, H_g), 3.54 and 3.56 (two s, 3, NCH_3), 2.28 (m, 1, H_e), 2.14 (s, 3, aromatic-CH_3),

1.60 (d of d, 1, J_{fe} = 13.5 Hz, J_{fg} = 3 Hz, H_f).]

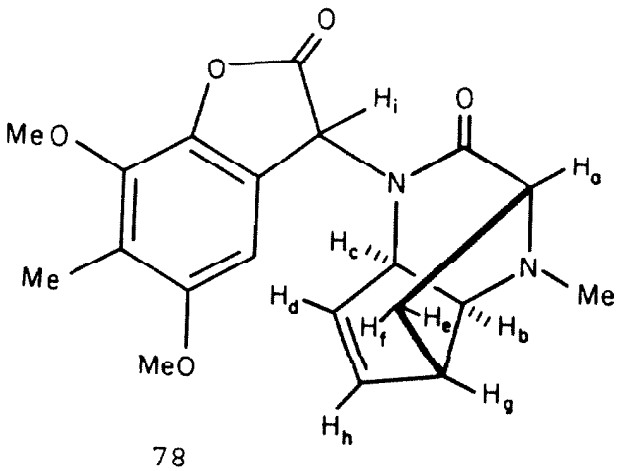
A solution of the crude hydrochloride of 77b prepared above in 6 mL of dichloromethane was added dropwise over 12 min to a stirred suspension of 500 mg (1.95 mmol) of silver(I) trifluoromethanesulfonate in 3 mL of dichloromethane under argon. After 30 min at room temperature, 10 mL of dichloromethane and 4 mL of brine was added, and the two-phase mixture was stirred rapidly for 5 min. The insoluble silver salts were removed by filtration through celite and the filtrate was partitioned between dichloromethane and 2 M aqueous Na_2CO_3. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give 176 mg of a blue oil. The crude product was purified by flash chromatography on 15 g of silica gel (55:45 acetone:dichloromethane) to afford 105.1 mg (58%) of pure lactone 78 as a white solid. ^1H NMR indicated that this material was an approximately 1.5:1 mixture of isomers at position 9: mp 195-196.5°C; IR ($CHCl_3$) 3018, 2960, 1810 (shoulder at 1825), 1660, 1611, 1470, 1425, 1341, 1309, 1140, 1070, 1018, 975, 937, 905, 885, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.37 (s, 1, aromatic-H), 6.03 and 6.22 (two m, 2, H_d, H_h), 5.53 (br, H_i, major isomer), 5.34 (br s, H_i, minor isomer), 4.18 (d of d, 1, J_{cb} = 6 Hz, J_{cd} = 2.5 Hz, H_c), 3.95

(s, 3, $OC\underline{H}_3$), 3.87 (t, 1, $J_{bc} = J_{bg} - 6$ Hz, H_b), 3.70 (s, 3, $OC\underline{H}_3$), 3.53 (m, 1, H_a), 3.00 (m, 1, H_g), 2.63 (s, 3, $NC\underline{H}_3$), 2.27 (m, 1, H_e), 2.10 (s, 3, aromatic-$C\underline{H}_3$), 1.51 (d of m, 1, J_{fe} = 13 Hz, H_f).

Exact mass calcd. for $C_{20}H_{22}N_2O_5$: 370.153. Found: 370.153.



77b

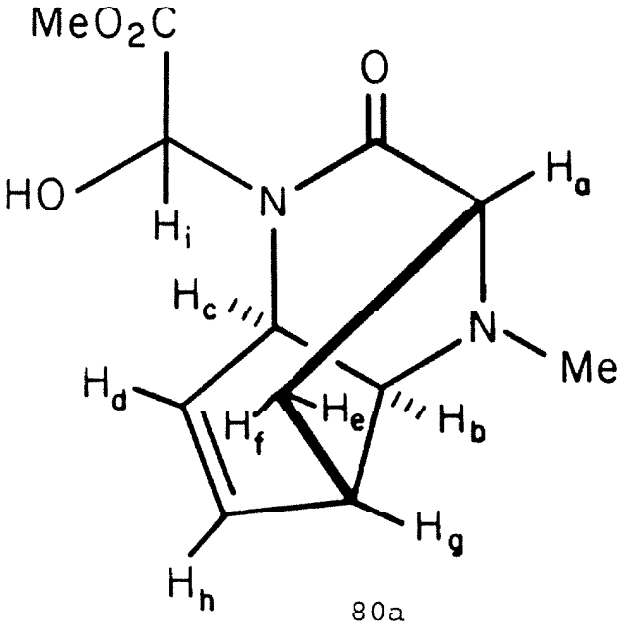


78

Methyl [2α,4(S*) and 4(R*),4aβ,7α,7aβ]-1,2,3,4a,7,7a-Hexahydro-α-hydroxy-1-methyl-3-oxo-2,7-methano-4H-cyclopentapyrazine-4-acetate (80a). Polymeric and partially hydrated methyl glyoxalate, prepared according to the method of Kelly,[65] was freshly distilled from phosphorous pentoxide (50°C, 25 mm). The distillate was collected in a flask cooled to -78°C and was warmed to room temperature immediately before use. ^{1}H NMR indicated that the distillate was >80% "free" methyl glyoxalate: ^{1}H NMR ($CDCl_3$) δ 9.42 (s, 1, $C\underline{H}O$), 3.90

(s, 3, OCH_3).

A solution of 139.0 mg (0.847 mmol) of 21 and 103.5 mg (1.170 mmol) of methyl glyoxalate (>80% "free") in 4 mL of dichloromethane was allowed to stir for 3 h at room temperature under argon. The solution was concentrated in vacuo and purified by flash chromatography on 21 g of silica gel packed in 96:4 dichloromethane: methanol. The column was eluted with 94:6 dichloromethane: methanol (fractions 1-15) followed by 91:9 dichloromethane methanol (fractions 16-40), collecting approximately 10-mL fractions. Fractions 14-23 were combined to afford 204.5 mg (96%) of 80a as a colorless oil. ^1H NMR indicated that this material was a 2:1 mixture of isomers at position 9: IR (CH_2Cl_2) 3515, 3060, 2960, 2807, 1755, 1660, 1450, 1340, 1305, 1260, 1225, 1165, 1138, 1095, 968, 905, 871 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.07 (m, 2, H_d, H_h), 5.66 (br s, H_i, minor isomer), 5.22 (br s, H_i, major isomer), 4.85 (br, 1, OH), 4.32 (d of d, J_{cd} = 2.3 Hz, J_{cb} = 6.5 Hz, H_c, major isomer), 4.18 (d of m, J_{cb} = 6.5 Hz, H_c, minor isomer), 3.90 (m, 1, H_b), 3.78 (s, 3, OCH_3), 3.50 (m, 1, H_a), 3.02 (m, 1, H_g), 2.58 (s, NCH_3, major isomer), 2.55 (s, NCH_3, minor isomer), 2.25 (d of c of d, 1, J_{ea} = 8 Hz, J_{eg} = 11 Hz, J_{ef} = 13 Hz, H_e), 1.48 (d of d, 1, J_{fg} = 3 Hz, J_{fe} = 13 Hz, H_f).



80a

Methyl [2α,4(S*),4aβ,7α,7aβ]-1,2,3,4a,7,7a-Hexahydro-α-(2-hydroxy-3,5-dimethoxy-4-methylphenyl)-1-methyl-3-oxo-2,7-methano-4H-cyclopentapyrazine-4-acetate (18), the Corresponding [2α,4(R*),4aβ,7α,7aβ]-Isomer (79) and Methyl [2α,4(S*) and 4(R*),4aβ,7α,7aβ)-α-(2,4-Dimethoxy-3-methylphenoxy)-1,2,3,4a,7,7a-hexahydro-1-methyl-3-oxo-2,7-methano-4H-cyclopentapyrazine-4-acetate (81). To a stirred solution of 204.5 mg (0.81 mmol) of 80a in 4mL of dichloromethane protected with a $CaSO_4$ drying tube was added 0.12 mL (1.69 mmol) of thionyl chloride. After 2 h at room temperature, the solution was partitioned between 35 mL of dichloromethane and 6 mL of 1:1 2 M aqueous Na_2CO_3:brine. The aqueous layer was re-extracted with 10 mL of dichloromethane and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 236 mg of chloride 80b as a colorless oil. ^1H NMR indicated that this material was a 1:1 mixture of isomers at postion 9: IR (CH_2Cl_2) 3060, 2960, 2818, 1770, 1680, 1440, 1420, 1410, 1345, 1265, 1200, 1181, 1171, 1151, 1143, 1117, 1076, 1042, 1000, 895 cm^{-1}; ^1H NMR $CDCl_3$) δ 6.48 and 6.57 (two s, 1, H_i), 5.84 and 6.14 (two m, 2, H_d, H_h), 4.34 and 4.48 (two d of d, 1, J_{cd} = 2.5 Hz, J_{cb} = 6.5 Hz, H_c), 3.90 (t, 1, $J_{bc} = J_{bg}$ = 6.5 Hz, H_c), 3.77 and 3.81 (two s, 3, OCH_3), 3.59 (d, 1, J_{ae} = 7.5 Hz, H_a), 3.00 (m, 1 H_g), 2.53

and 2.55 (two s, 3, NCH_3), 2.28 (d of d of d, 1, J_{ea} = 7.5 Hz, J_{eg} = 10.5 Hz, J_{ef} = 13 Hz, H_e), 1.49 (br d, 1, J_{fe} = 13 Hz, H_f).

To a bright orange, stirred solution of 178 mg (1.05 mmol) of phenol 19a and 0.25 mL (2.12 mmol) of tin tetrachloride in 9 mL of dichloromethane at 0°C under argon was added a solution of the crude chloride 80b (prepared above) in 3 mL of dichloromethane. A yellow-orange precipitate formed upon addition of the chloride. The stirred suspension was allowed to warm to room temperature for 40 h. Dichloromethane (20 mL) and 12 mL of 1:1 2 M Na_2CO_3:brine was added and the two-phase mixture was stirred rapidly for 5 min. The insoluble solids were removed by filtration through celite, and the filter cake was washed with 20 mL of dichloromethane. The organic layer was separated, the filter cake was washed with an additional 40 mL of dichloromethane, and the filtrate was employed to wash the original aqueous layer. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford 369 mg of a pale yellow oil. A preliminary separation of this mixture was carried out by MPLC on a LoBar size B column equilibrated with 99:1 dichloromethane:methanol. The column was eluted with 96:4 dichloromethane:methanol,

collecting approximately 10-mL fractions. Fractions 44-46 afforded 99 mg of a mixture of 19a, 79, 80c and 81. Fractions 47-62 afforded 183.2 mg (56% overall from 80a) of 18 as an amorphous foam, which upon the addition of ether, crystallized to give a white solid [mp 166.5-169.5°C (dec)]. An analytical sample of 18 was prepared by recrystallization from dichloromethane/ether [mp 177.5-179°C (dec)].

Fractions 44-46 were further separated by MPLC on a LoBar size B column equilibrated with dichloromethane. The column was eluted with 97.5:2.5 dichloromethane:methanol (fractions 1-45), 97:3 dichloromethane:methanol (fractions 46-95) and finally 96:4 dichloromethane:methanol (fractions 96-160), collecting approximately 10 mL fractions. Fractions 48-63 gave 36.4 mg (11%) of aryl ether 81 as a colorless oil [3:1 mixture of isomers at C(9), by ^{1}H NMR]. Fractions 72-90 gave 10.1 mg (5%) of methyl ether 80c (X = OCH_3) as a colorless oil [1.2:1 mixture of isomers at C(9), by ^{1}H NMR]. Fractions 117-133 afforded 35.6 mg (10%) of 79 as a colorless oil. These are overall yields based on 80a.

In a separate experiment, ether was added to the crude amidoalkylation product, inducing the crystalliza-

tion of pure 18 [mp 178-179.5 °C (dec)] in 48% overall yield (three steps) from tricyclic lactam 21.

18: IR (CH_2Cl_2) 3540, 3060, 2960, 1755, 1650, 1490, 1465, 1418, 1310, 1250, 1190, 1170, 1128, 1020, 994 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.48 (s, 1, aromatic-H), 6.02 (d of d, 1, J_{hg} = 3 Hz, J_{hd} = 6 Hz, H_h), 6.0-7.0 (br, 1, OH), 5.91 (s, 1, H_i), 5.83 (d of d, 1, J_{dc} = 1.8 Hz, J_{dh} = 6 Hz, H_d), 3.78 (s, 3, OCH_3), 3.73 (s, 6, two OCH_3's), 3.6-4.0 (m, 2, H_c, H_b), 3.59 (d, 1, J_{ae} = 8 Hz, H_a), 2.93 (m, 1, H_g), 2.53 (s, 3, NCH_3), 2.17 (s, 3, aromatic-CH_3), 2.1-2.4 (m, 1, H_e), 1.55 (d of d, 1, J_{fg} = 3 Hz, J_{fe} = 13 Hz, H_f); ^{13}C NMR ($CDCl_3$) δ 172.5, 170.5, 151.4, 146.5, 142.5, 136.8, 133.5, 121.3, 117.0, 107.7, 68.9, 66.6, 60.8, 57.3, 57.1, 56.1, 52.3, 45.0, 35.0, 32.2, 9.42.

Anal. calcd. for $C_{21}H_{26}N_2O_6$: C, 62.67; H, 6.51; N, 6.96. Found: C, 62.81; H, 6.58; N, 6.85.

Exact mass calcd. for $C_{21}H_{26}N_2O_6$: 402.179. Found: 402.178.

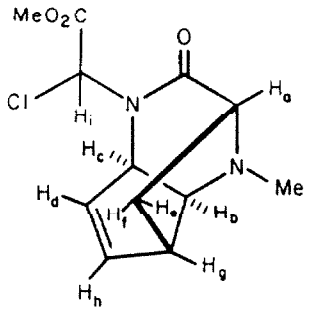
79: IR ($CHCl_3$) 3540, 3020, 2960, 1745, 1640, 1466, 1419, 1340, 1307, 1220, 1170, 1131 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.52 (s, 1, aromatic-H), 6.0-7.0 (br, 1, OH), 5.96 (s, 1, H_i), 5.88 (d of d, 1, J_{hg} = 3 Hz, J_{hd} = 6 Hz, H_h), 5.06 (d of d, 1, J_{dc} = 2.7 Hz, J_{dh} = 6 Hz, H_d), 4.39

(d of d, 1, J_{cd} = 2.7 Hz, J_{cb} = 6.5 Hz H_c), 3.82 (m, 1, H_b), 3.78 (s, 3, OCH_3), 3.72 (s, 6, two OCH_3's), 3.61 (d, 1, J_{ae} = 7.5 Hz, H_a), 2.84 (m, 1, H_g), 2.68 (s, 3, NCH_3), 2.17 (s, 3, aromatic-CH_3), 2.1-2.4 (m, 1, H_e), 1.45 (d of d, 1, J_{fg} = 3 Hz, J_{fe} = 13 Hz, H_f); ^{13}C NMR ($CDCl_3$) δ 173.6, 171.1, 151.6, 146.8, 142.7, 138.3, 132.8, 121.7, 117.3, 107.8, 68.8, 66.5, 60.7, 57.6, 56.1, 55.6, 52.4, 45.1, 35.2, 32.8, 9.4.

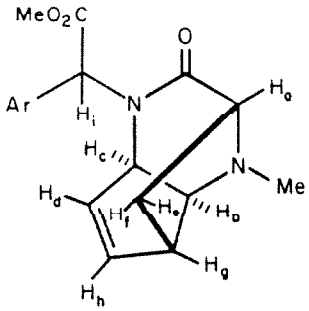
Exact mass calcd. for $C_{21}H_{26}N_2O_6$: 402.179. Found: 402.180.

81: IR ($CHCl_3$) 3025, 2960, 1762, 1660, 1605, 1487, 1440, 1200, 1160, 1117, 928 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.81 (d, 1, J = 9 Hz, aromatic-H), 6.69 (s, H_i, minor isomer), 6.65 (s, H_i, major isomer), 6.46 (d, J = 9 Hz, aromatic-H, major isomer), 6.45 (d, J = 9 Hz, aromatic-H, minor isomer), 6.08 (d of d, 1, J_{hg} = 3 Hz, J_{hd} = 6 Hz H_h), 5.96 (d of d, J_{dc} = 3 Hz, J_{dh} = 6 Hz, H_d, minor isomer), 5.72 (d of d, J_{dc} = 3 Hz, J_{dh} = 6 Hz, H_d, major isomer), 4.53 (d of d, J_{cd} = 3 Hz, J_{cb} = 6 Hz, H_c, major isomer), 4.28 (d of d, J_{cd} = 3 Hz, J_{cb} = 6 Hz, H_c, minor isomer), 3.7-4.0 (m, 10, H_b and three OCH_3's), 3.4-3.7 (m, 1, H_a), 2.97 (m, 1, H_g), 2.58 (s, NCH_3, minor isomer), 2.33 (s, NCH_3, major isomer), 2.12 (s, 3, aromatic-CH_3), 2.1-2.5 (m, 1, H_e), 1.54 (d of d, 1, J_{fg} = 3 Hz, J_{fe} = 13 Hz, H_f).

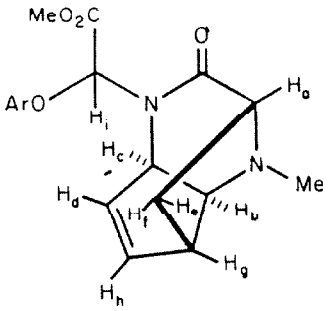
Exact mass calcd. for $C_{21}H_{26}N_2O_6$: 402.179. Found: 402.178.



80b



18, α-H_i
79, β-H_i



81

Cleavage of Lactone 78 With Methanol to Afford 18 and 79. A stirred solution of 35.8 mg (0.097 mmol) of lactone 78 in 3 mL of methanol was heated to reflux for 1.5 h. The solvent was removed at reduced pressure to afford a thick oil. ^{1}H NMR indicated that this material was a 1:1 mixture of 18 and 79.

Sodium Methoxide Catalyzed Isomerization of 18. To a stirred solution of 19.5 mg (0.049 mmol) of 18 in 1 mL of methanol at 0°C under argon was added 12.5 mg (0.23 mmol) of sodium methoxide. After 3 h at 0°C, the solution was partitioned between dichloromethane and brine. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford 18.5 mg of a colorless oil.

^{1}H NMR indicated that this material was an approximately 1.6:1 mixture of 79:18.

Tin Tetrachloride Promoted Rearrangement of Aryl Ether 81. To a stirred solution of 36 mg (0.089 mmol) of 81 in 2.5 mL of dichloromethane at 0°C under argon was added 0.20 mL (0.20 mmol) of 1 M tin tetrachloride in dichloromethane. After 5 min at 0°C, the yellow solution was allowed to warm to room temperature for 12 h. During this period, the solution turned dark and a precipitate formed. As judged by TLC (92.5:7.5 dichloromethane:methanol), the reaction appeared to proceed to partial conversion and then halt. An additional 0.10 mL (0.10 mmol) of 1 M tin tetrachloride in dichloromethane was added, and the suspension was allowed to stir at room temperature for 10 h. The reaction did not appear to progress further during this period (TLC). Dichloromethane and 5 mL of 1:1 2 M aqueous Na_2CO_3:brine were added, and the two-phase mixture was stirred rapidly for 5 min. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to afford 29 mg of a colorless oil. The crude mixture was separated via MPLC (LoBar size A column), eluting with 98:2 dichloromethane:methanol (fractions 1-30) followed by 96:4 dichloromethane:methanol (fractions

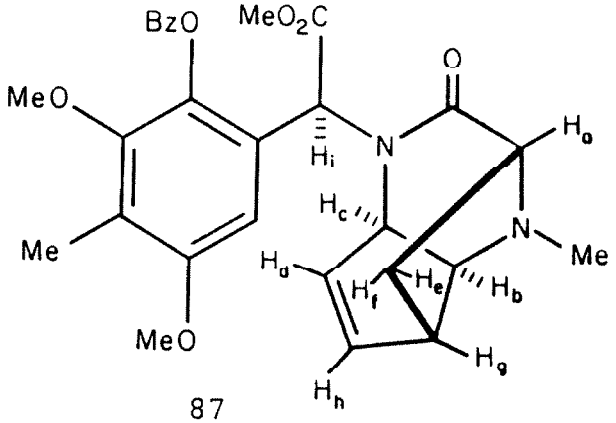
31-60) and collecting 4 mL fractions. Fractions 18-25 gave 14.4 mg (40%) of recovered 81 as a colorless oil [1:1.5 mixture of isomers at C(9)].[83] Fractions 39-52 gave 9.8 mg (27%) of a pale yellow oil. ^{1}H NMR indicated that this material was a mixture of 18 and 79 in an 86:14 ratio, respectively.

Methyl [2α,4(S*),4aβ,7α,7aβ]-α-(2-Benzoyloxy-3,5-dimethoxy-4-methylphenyl)-1,2,3,4a,7,7a-hexahydro-1-methyl-3-oxo-2,7-methano-4H-cyclopentapyrazine-4-acetate (87).

To a stirred solution of 105.1 mg (0.261 mmol) of phenol 18 in 2 mL of pyridine under argon was added 61 μl (0.522 mmol) of benzoyl chloride. After 14 h at room temperature, 0.5 mL of methanol was added in order to quench the excess benzoyl chloride. The solution was allowed to stir for 10 min and was then concentrated in vacuo. The residue was dissolved in 40 mL of dichloromethane and this solution was washed with 5 mL of 1:1 2 M aqueous Na_2CO_3:brine. The aqueous layer was re-extracted with 10 mL of dichloromethane and the combined organic layers were dried (Na_2SO_4) and evaporated at reduced pressure to afford a thick oil. Flash chromatography on 18 g of silica gel, packed in 99:1 dichloromethane:methanol and eluted with 97:3 dichloromethane:methanol, gave 129.7 mg (98%) of pure 87 as a thick, colorless oil:

IR (CH_2Cl_2) 3050, 2983, 2955, 1750, 1650, 1601, 1590, 1450, 1410, 1340, 1306, 1250, 1220, 1175, 1130, 1051, 1022, 890 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (m, 2, ortho-benzoyl-H), 7.53 (m, 3, meta- and para-benzoyl-H), 6.60 (s, 1, aromatic-H), 5.98 (d of d, 1, J_{hg} = 3 Hz, J_{hd} = 6 Hz, H_h), 5.78 (d of d, 1, J_{dc} = 2.5 Hz, J_{dh} = 6 Hz, H_d), 5.60 (s, 1, H_i), 3.90 (d of d, 1, J_{cd} = 2.5 Hz, J_{cb} = 6 Hz, H_c), 3.78 (s, 3, OCH_3), 3.68 (s, 6, two OCH_3's), 3.6-3.8 (m, 1, H_b), 3.48 (d, 1, J_{ae} = 7.5 Hz, H_a), 2.90 (m, 1, H_g), 2.40 (s, 3, NCH_3), 2.18 (s, 3, aromatic-CH_3), 2.0-2.4 (m, 1, H_e), 1.50 (d of d, 1, J_{fg} = 3 Hz, J_{fe} = 13 Hz, H_f).

Exact mass calcd. for $C_{28}H_{30}N_2O_7$: 506.2053. Found: 506.2065.



87

Methyl [2α,4(S*),4aβ,5α,7β,8α,8aβ]-α-(2-Benzoyloxy-3,5-dimethoxy-4-methyl)-octahydro-5-hydroxy-7-methoxy-1-methyl-3-oxo-2,8-methano-4H-pyrano[3,4-b]pyrazine-4-

acetate (88a), the Corresponding [2α,4(S*),4aβ,5β,7β,8α,8aβ]-stereoisomer (88b) and the Corresponding 5-Methoxy-7-hydroxy-regioisomer (89). To 71.3 mg (0.14 mmol) of 87 in 4 mL of dichloromethane was added 1 mL of ether saturated with anhydrous hydrochloric acid gas. The solution was concentrated in vacuo, and the solid which remained was triturated with 4 mL of ether. The solvent was evaporated at reduced pressure to afford 70.0 mg (92%) of the corresponding hydrochloride salt as a white, sticky solid.

A stirred solution of 24.0 mg (0.044 mmol) of the hydrochloride salt of benzoate 87 in 4 mL of methanol containing 14 drops of a saturated methanolic solution of Sudan III,[66] protected with a $CaSO_4$ drying tube and maintained at -78°C, was bubbled with a dilute stream of ozone in oxygen until the red color of the dye discharged (6 min). The solution was then bubbled with nitrogen for 12 min to remove any excess ozone, and 7 mg of 5% palladium on carbon was added. The stirred suspension was placed under 1 atm of hydrogen and was allowed to warm to 0°C for 1 h. After removing the catalyst by filtration through celite, the filtrate was concentrated in vacuo and partitioned between 30 mL of dichloromethane and 4 mL of 1:1 2 M aqueous Na_2CO_3:brine. The organic

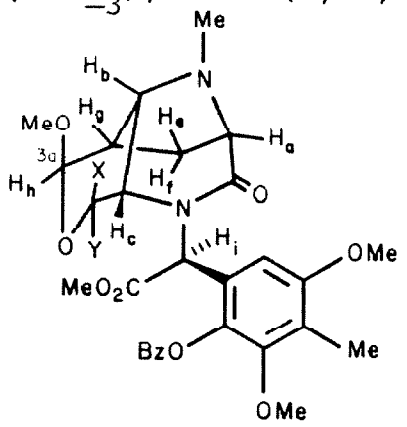
layer was dried (Na_2SO_4) and evaporated at reduced pressure to give 23 mg of a mixture of tetrahydropyranols as a pale yellow oil. The major component, as judged by ^1H NMR and TLC (90:10 dichloromethane:methanol), was isolated via flash chromatography on 6 g of silica gel (packed in 99:1 dichloromethane:methanol, eluted with 97:3 dichloromethane:methanol), affording 17.7 mg (70%) of a mixture of 88a and 88b (88a:88b ~ 1:1 by ^1H NMR[69]). This mixture appeared as a single, homogeneous spot on TLC.

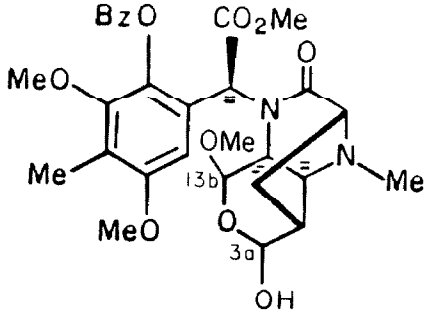
In a separate experiment, the minor, more polar coproduct was isolated (~18% yield) by flash chromatography. Structure 89 has been tentatively assigned to this coproduct. ^1H NMR and TLC indicates that this material is a mixture of two stereoisomers.

88a,b: IR (CH_2Cl_2) 3700, 3560, 3300, 2990, 2960, 2850, 1755 (shoulder at 1735), 1670, 1602, 1590, 1450, 1411, 1250, 1218, 1176, 1130, 1102, 1089, 1065, 1025, 1015, 960, 892 cm^{-1}; ^1H NMR[69] ($CDCl_3$) δ 8.20 (m, 2, ortho-benzoyl-H), 7.60 (m, 3, meta- and para-benzoyl-H), 6.62 (s, aromatic-H, 88a), 6.57 (s, aromatic-H, 88b), 5.47 (s, H_i, 88a), 5.23 (d, J_{dj} = 7.5 Hz, H_d, 88b), 5.08 (s, H_i, 88b), 4.95 (d, J_{dj} = 8.5 Hz, H_d, 88a), 4.83 (s, H_h, 88b), 5.79 (s, H_h, 88a), 3.48 (s, 3a-OCH_3, 88b),

3.34 (s, 3a-OCH_3, 88a), 3.0-4.1 (m, 13, three OCH_3's, H_a, H_b, H_c, H_j), 2.61 (s, NCH_3, 88b), 2.52 (s, NCH_3, 88a), 2.3-2.7 (m, H_g, H_e), 2.19 (s, 3, aromatic-CH_3), 1.70 (m, 1, H_f).

89: ^1H NMR ($CDCl_3$) 6.57 and 6.53 (two s, 1, aromatic-H), 3.03 and 2.98 (two s, 3, 13b-OCH_3), 2.64 (s, 3, NCH_3), 2.15 (s, 3, aromatic-CH_3).





88a, X = H, Y = OH
88b, X = OH, Y = H

89

(2α,5β,7aβ,9β,10α,10aβ,10bβ)-5-(2-Benzoyloxy-3,5-dimethoxy-4-methylphenyl)-hexahydro-9-methoxy-1-methyl-2,10-methano-7,8-dioxa-1,4-diazaphenalene-3,6(1H,2H)-dione (90). To a stirred solution of 16.0 mg (0.028 mmol) of 88a,b in 2 mL of dichloromethane at -78°C under argon was added 0.24 mL (0.06 mmol) of 0.25 M tin tetrachloride in dichloromethane to afford a white suspension. After 40 min at -78°C, the reaction mixture was allowed to warm to 0°C for 1 h, followed by room temperature

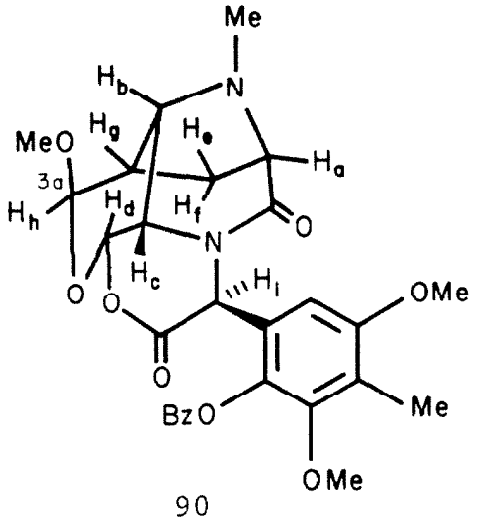
for 1 h. As judged by TLC (90:10 dichloromethane: methanol), the reaction appeared to proceed to partial conversion and then halt. The suspension was recooled to 0°C and 0.12 mL (0.03 mmol) of 0.25 M tin tetrachloride in dichloromethane was added. After 30 min at 0°C, the reaction mixture was allowed to warm to room temperature for 1 h. The reaction did not appear to progress further during this period (TLC). The suspension was diluted with dichloromethane and then quenched with 1.5 mL of 2 M aqueous Na_2CO_3. After stirring the two-phase mixture rapidly for 5 min, 2 mL of brine was added. The organic layer was separated, dried (Na_2SO_4) and concentrated in vacuo to give 16 mg of a pale yellow oil. The crude mixture was separated by MPLC on a LoBar size A column equilibrated with dichloromethane. The column was eluted with 98:2 dichloromethane:methanol and approximately 4 mL fractions were collected. Fractions 18-20 gave 5.3 mg of lactone 90 as a viscous oil. An analytical sample of 90 was prepared by crystallization from ether. Fractions 30-51 gave 4.4 mg of recovered 88a,b as a colorless oil.

90: mp 218-219°C; IR (CH_2Cl_2) 3060, 2960, 2860, 1770, 1750, 1675, 1600, 1450, 1388, 1245, 1221, 1175, 1160, 1100, 1083, 1060, 1022, 981, 970, 936, 891 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 8.19 (m, 2, ortho-benzoyl-H), 7.59 (m, 3, meta- and para-benzoyl-H), 6.93 (s, 1, aromatic-H), 6.27 (s, 1, H_i), 5.23 (br s, 1, H_d), 4.79 (s, 1, H_h), 4.15 (m, 1, H_c), 3.81 (s, 3, OCH_3), 3.59 (s, 3, OCH_3), 3.35 (s, 3, OCH_3), 3.3-3.7 (m, 2, H_a, H_b), 2.31 (s, 3, NCH_3), 2.2-2.6 (m, 2, H_e, H_g), 2.14 (s, 3, aromatic-CH_3), 1.70 (m, 1, H_f); ^{13}C NMR ($CDCl_3$)[84] δ 156.2, 136.0, 133.9, 130.3, 128.8, 126.9, 122.6, 108.5, 101.7, 91.4, 63.4, 61.0, 56.8, 55.9, 55.8, 52.4, 45.4, 37.9, 34.6, 32.8, 9.4.

Anal. calcd. for $C_{28}H_{30}N_2O_9$: C, 62.44; H, 5.62; N, 5.20. Found: C, 62.20; H, 5.70; N, 5.08.

Exact mass calcd. for $C_{28}H_{30}N_2O_9$: 538.197. Found: 538.197.



90

Methyl (2α,3β,3aα,5β,8β,12bα,12cα)-9-Benzoyloxy-2,3,3a,4,5,6,12b,12c-octahydro-2,10,12-trimethoxy-4,11-

dimethyl-6-oxo-3,5-methano-8H-1-oxa-4,7-diazabenz[d,e]-anthracene-8-carboxylate (92). To a solution of 128.0 mg (0.252 mmol) of benzoate 87 in 5 mL of dichloromethane was added 1 mL of ether saturated with anhydrous hydrochloric acid gas. The resulting solution was concentrated in vacuo and the residue was twice redissolved in 5 mL of dichloromethane and concentrated in vacuo to provide the hydrochloride salt of 87 as an amorphous foam.

A stirred solution of the hydrochloride salt in 14 mL of methanol containing 0.5 mL of a saturated methanolic solution of Sudan III,[66] protected with a $CaSO_4$ drying tube and maintained at -78°C, was bubbled with a dilute stream of ozone in oxygen until the red color of the dye discharged (13 min). The solution was then bubbled with nitrogen for 15 min to remove any excess ozone, and 30 mg of 5% palladium on carbon was added. The stirred suspension was placed under 1 atm of hydrogen and was allowed to warm to 0°C for 1.5 h followed by room temperature for 40 min. The catalyst was removed by filtration through celite, the collected solids were washed with methanol followed by dichloromethane, and the filtrate was concentrated in vacuo. The residue was partitioned between 40 mL of dichloromethane and 5 mL of 1:1 2 M aqueous Na_2CO_3:brine.

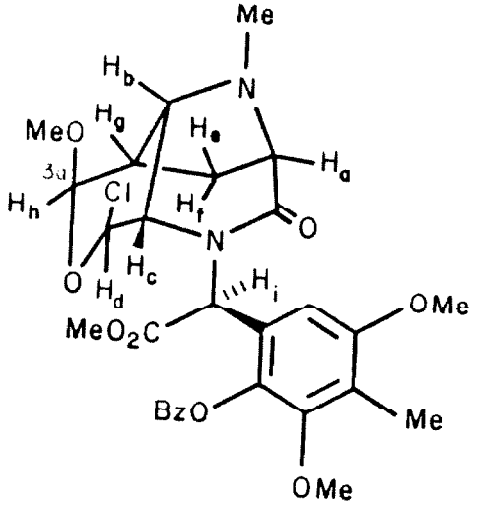
The aqueous phase was re-extracted with 10 mL of dichloromethane and the combined organic layers were dried (Na_2SO_4) and evaporated at reduced pressure to afford 170 mg of a mixture of tetrahydropyranols.

To a stirred solution of the crude tetrahydropyranols and 0.80 mL (8.3 mmol) of carbon tetrachloride in 5 mL of dichloromethane at -78°C under argon was added 60 µl (0.33 mmol) of hexamethylphosphorous triamide. After 15 min at -78°C, the solution was allowed to warm to room temperature for 1 h. [In a separate experiment which employed chromatographically purified 88a,b, this solution was concentrated in vacuo to afford a pale yellow oil. ^1H NMR indicated that the crude chloride was largely, if not exclusively, a single stereoisomer: ^1H NMR ($CDCl_3$) δ 8.16 (m, 2, ortho-benzoyl-H), 7.60 (m, 3, meta- and para-benzoyl-H), 6.56 (s, 1, aromatic-H), 6.26 (s, 1, H_d), 5.51 (s, 1, H_i), 4.96 (s, 1, H_h), 3.2-4.3 (m, 15, H_a, H_b, H_c and four OCH_3 singlets at δ 3.42, 3.68, 3.70 and 3.83), 2.3-3.2 (m, H_e, H_g, NCH_3, HMPA and other minor phosphorous containing impurities), 2.20 (s, 3, aromatic-CH_3), 1.79 (m, 1, H_f)]. The stirred solution was recooled to -78°C and 103 µl (0.882 mmol) of tin tetrachloride was added. After 5 min at -78°C, the reaction mixture was allowed to warm to 0°C

for 1 h. Dichloromethane (25 mL) and 6 mL of 1:1 2 M aqueous Na_2CO_3:brine was added, and the two-phase mixture was rapidly stirred for 5 min. The organic layer was diluted with 25 mL of dichloromethane and then separated. The aqueous layer, which contained much suspended inorganic salts, was filtered through celite and the collected solids were washed with 50 mL of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford a pale orange oil. The crude product was purified by MPLC on a LoBar size B column equilibrated with dichloromethane. The column was eluted with 97:3 dichloromethane:methanol (fractions 1-56), 96:4 dichloromethane:methanol (fractions 57-83) and finally 95:5 dichloromethane:methanol (fractions 84-120), collecting approximately 10-mL fractions. Fractions 71-89 gave 58.7 mg (42%, overall from 87) of 92, as an off-white solid (mp 221.5-223.5°C). Single crystals suitable for X-ray crystallography were prepared by the vapor diffusion of ether into a benzene solution of 92. An analytical sample of 92 was prepared by recrystallization from tetrahydrofuran/ether, again employing the vapor diffusion technique: mp 225-227°C; IR (CH_2Cl_2) 3060, 2990, 2955, 2840, 1750, 1668, 1603, 1580, 1451, 1433, 1358, 1313, 1242, 1200, 1175, 1124,

1085, 1065, 1022, 1000, 964, 940, 891 cm^{-1}; ^1H NMR ($CDCl_3$, 34°C) δ 8.29 (m, 2, ortho-benzoyl-H), 7.63 (m, 3, meta- and para-benzoyl-H), 5.57 (br, 1, H_i), 5.12 (s, 1, H_d), 5.02 (s, 1, H_h), 3.87 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 3.61 (s, 3, OCH_3), 3.1-4.1 (m, 6, H_a, H_b, H_c, OCH_3), 2.50 (s, 3, NCH_3), 2.29 (s, 3, aromatic-CH_3), 1.9-2.8 (m, 3, H_e, H_f, H_g); ^{13}C NMR ($CDCl_3$) δ 172.2, 168.2, 164.0, 156.0, 152.5, 138.3, 133.7, 130.3, 129.1, 128.6, 126.0, 123.5, 123.0, 101.2, 64.3, 62.3, 60.8, 59.1, 58.2, 55.6, 54.0, 52.4, 50.3, 38.5, 35.5, 32.3, 10.1.

Anal. calcd. for $C_{29}H_{32}N_2O_9$: C, 63.03; H, 5.84; N, 5.07. Found: C, 63.07; H, 5.95; N, 4.93.



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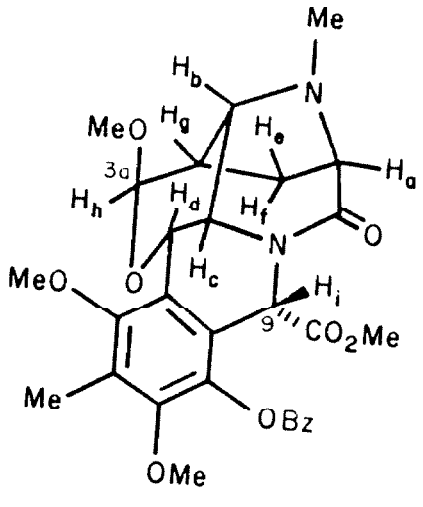

92

Methyl (2α,3β,3aα,5β,8β,12bα,12cα)-2,3,3a,4,5,6,12b,12c-Octahydro-9-hydroxy-2,10,12-trimethoxy-4,11-dimethyl-6-oxo-3,5-methano-8H-1-oxa-4,7-diazabenz[d,e]anthracene-8-carboxylate (93). To a stirred solution of 36.6 mg (0.066 mmol) of benzoate 92 in 3 mL of 1:1 tetrahydrofuran:methanol was added 0.25 mL (0.25 mmol) of 1 M aqueous NaOH. After 4.5 h at room temperature, the solvents were evaporated at reduced pressure and the residue was partitioned between 30 mL of dichloromethane and 3 mL of 2:1 brine:water. The aqueous phase was re-extracted with 10 mL of dichloromethane and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford 22.2 mg of crude 93. The aqueous phase was adjusted to pH 8 and was extracted with two 20-mL portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford an additional 9.2 mg of crude 93. These two fractions were combined and purified by flash chromatography on 6 g of silica gel, packed in 99.5:0.5 dichloromethane:methanol and eluted with 96:4 dichloromethane:methanol, to give 24.9 mg (84%) of a sticky white solid. An analytical sample of 93 was prepared via recrystallization from dichloromethane/ether: mp 195-196°C (dec); IR (neat) 3700-2800 (broad), 1745, 1665, 1608, 1468, 1440,

1352, 1300, 1175, 1128, 1109, 1083, 1061, 1016, 1000, 961, 940, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz, see Table 9); ^{13}C NMR ($CDCl_3$) δ 172.4, 171.0, 150.8, 148.7, 144.0, 125.4, 121.9, 115.9, 101.2, 64.4, 62.1, 60.4, 59.0, 58.4, 55.4, 54.1, 53.1, 50.5, 38.5, 35.7, 32.4, 9.9.

Anal. calcd. for $C_{22}H_{28}N_2O_8$: C, 58.92; H, 6.29; N, 6.25. Found: C, 58.65; H, 6.43; N, 5.93.

Exact mass calcd. for $C_{22}H_{28}N_2O_8$: 448.1845. Found: 448.1853.

When the infrared spectrum of 93 was recorded in dichloromethane, a new carbonyl stretch appeared at 1700 cm^{-1} with a concomittant decrease in intensity of the stretch at 1745 cm^{-1}.

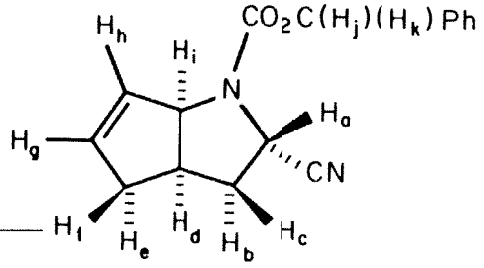

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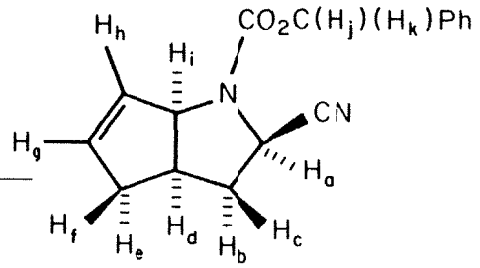
Table 5. 500 MHz ^{1}H NMR Spectral Data for Bicyclic Nitrile 38.[a]

Proton[b]	Chemical Shift (δ)[c]	Coupling Constant (Hz) With H_a	H_b	H_c	H_d	H_e	H_f	H_g	H_h	H_i
H_a	4.56, 4.60	--	--	8	--	--	--	--	--	--
H_b	2.37	--	--	12.5	7.5	--	--	--	--	--
H_c	1.84	8	12.5	--	11	--	--	--	--	--
H_d	3.13	--	7.5	11	--	7.5	--	--	--	8
H_e	2.58	--	--	--	7.5	--	17	2.5	2.5	2.5
H_f	2.18	--	--	--	--	17	--	2.5	2.5	2.5
H_i	4.82, 4.87	--	--	--	8	2.5	2.5	2.5	2.5	--

[a] $CDCl_3$ solution. [b] Other signals (δ): aromatic H: 7.35 (m, 5H); H_g and H_h: 5.95 (d of q, 0.5H, J_{gh} = 5.5, J_q = 2.5), 5.78 (d of q, 0.5H, J_{gh} = 5.5, J_q = 2.2), 5.72 (two overlapping d of q, 1H, J_{gh} = 5.5, J_q = 2.5); H_j and H_k: 5.26 (d, 0.5H, J_{jk} = 12.5), 5.20 (s, 1H), 5.16 (d, 0.5H, J_{jk} = 12.5). [c] Two signals, one for each carbamate rotomer, are noted for all tabulated protons (except H_f, where they are coincident). The rotomers are present in nearly equal concentrations. For protons H_b through H_e, two overlapping multiplets are observed, and thus, the chemical shift reported is the center of these two signals. For protons H_a and H_i, two completely separate multiplets are observed, and thus, the chemical shift is reported for each signal.

Table 6. 500 MHz ^{1}H NMR Spectral Data for Bicyclic Nitrile 39.[a]

Proton[b]	Chemical Shift (δ)[c]	Coupling Constant (Hz) With H_a	H_b	H_c	H_d	H_e	H_f	H_i
H_a	4.60, 4.65	--	8.5	4	--	--	--	--
H_b	2.50	8.5	--	13	8.5	--	--	--
H_c	2.08	4	13	--	4	--	--	--
H_d	3.02	--	8.5	4	--	8.5	--	7.5
H_e	2.69	--	--	--	8.5	--	17	--
H_f	2.44	--	--	--	--	17	--	--
H_i	4.93, 4.99	--	--	--	7.5	--	--	--



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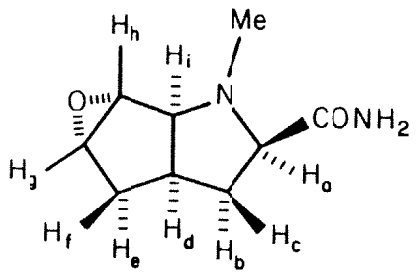
[a] $CDCl_3$ solution. [b] Other signals (δ): aromatic H: 7.36 (m, 5H); H_g and H_h: 5.94 (m, 0.5H), 5.87 (m, 1H), 5.80 (m, 0.5H); H_j and H_k: 5.26 (d, 0.5H, J_{jk} = 12.5), 5.25 (d, 0.5H, J_{jk} = 11.5), 5.22 (d, 0.5H, J_{jk} = 11.5), 5.21 (d, 0.5H, J_{jk} = 12.5). [c] Two signals, one for each carbamate rotomer, are noted for all tabulated protons (except H_b and H_f, where these signals are coincident). The rotomers are present in nearly equal concentrations. For protons H_c through H_e, two overlapping multiplets are observed, and thus, the chemical shift reported is the center of the two signals. For protons H_a and H_i, two completely separate multiplets are observed, and thus, the chemical shift is reported for each signal.



47b

Table 7. 500 MHz ^{1}H NMR Spectral Data for Epoxy Amide 47b in Chloroform-d Solution.

		Coupling Constant (Hz) With								
		H_a	H_b	H_c	H_d	H_e	H_f	H_g	H_h	H_i
H_a	3.12	--	10	7	--	--	--	--	--	--
H_b	2.51	10	--	14	10	--	--	--	--	--
H_c	1.64	7	14	--	4	--	--	--	--	--
H_d	2.42	--	10	4	--	8.5	8	--	--	7
H_e	2.30	--	--	--	8.5	--	15	--	--	--
H_f	1.52	--	--	--	8	15	--	2	--	--
H_g	3.53	--	--	--	--	--	2	--	2.5	--
H_h	3.48	--	--	--	--	--	--	2.5	--	--
H_i	3.22	--	--	--	7	--	--	--	--	--
CH_3	2.48									
NH	6.45 7.00									

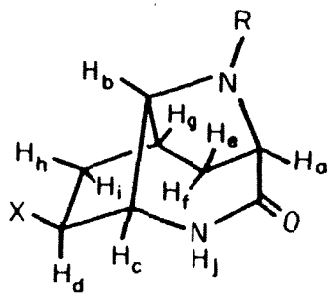
Table 8. ^{1}H NMR Spectral Data for Selected Tricyclic Intermediates.

	45[a,c]	50[a,c]	48b[b,d]	51[a,c]	52a[b,c]	46[a,c]	49b[b,d]	54b[b,c]	55[b,c]
					Chemical Shift (δ)				
H_a	4.37	4.53	3.38	3.39	3.34	4.50	3.39	3.44	3.18
H_b	4.94	4.90	3.91	3.89	4.06	4.38	3.61	3.97	3.38
H_c	3.73	3.73	3.76	3.99	3.82	3.40	3.44	3.58	4.11
H_d	4.07	-- [i]	4.18	4.93	3.63[m]	4.06	4.37	4.41	4.31
H_e	-- [j]	-- [k]	2.49	-- [l]	2.45	-- [n]	2.21	2.23	2.07
H_f	-- [j]	1.72	1.60	1.59	1.58	-- [n]	1.82	1.78	1.86
H_g	2.82	3.01	2.87	2.88	2.81	3.01	3.06	3.08	2.44
H_h	-- [j]	2.51	2.14	-- [l]	2.27	-- [n]	2.36	-- [o]	2.66
H_i	-- [j]	2.51	1.86	2.01	2.12	-- [n]	1.75	1.69	1.45
H_j	6.84	6.68	-- [p]	6.26	6.53	7.04	-- [p]	7.12	7.12
NCH_3	-- [i]	-- [i]	2.46	2.52	2.47	-- [i]	2.49	2.58	2.43
$ArCH_2$	5.09	5.16	-- [i]	-- [i]	-- [i]	5.10	-- [i]	-- [i]	-- [i]
ArH	7.32	7.36	-- [i]	-- [i]	-- [s]	7.30	-- [i]	-- [i]	-- [i]

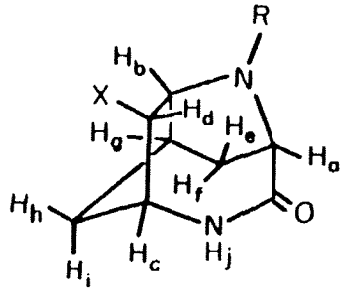
Table 8. Continued

	45[a,c]	50[a,c]	48b[b,d]	51[a,c]	52a[b,c,m]	46[a,c]	49b[b,d]	54b[b,c]	55[b,c,q]
					Coupling Constant (Hz)				
J_{ae}	7	7.5	6.5	6.5	6.5	6	6.5	6.5	7
J_{af}	-- [e]	-- [e]	-- [f]	-- [e]	-- [f]	-- [e]	-- [f]	-- [f]	1.5
J_{bc}	5	6	5	5.5	5	-- [e]	2[h]	2[h]	6.5
J_{bg}	8	7	7.5	6	7	6	6	6	-- [f]
J_{ch}	-- [e]	-- [e]	-- [f]	-- [g]	-- [f]	4.5	5	5.5	9
J_{cj}	-- [e]	2.5	-- [p]	-- [g]	1.8	7.5	-- [p]	7	5
J_{di}	4.5	-- [i]	5	5	7	-- [e]	-- [f]	-- [f]	-- [f]
J_{ef}	-- [g]	13.5	13.5	13.5	13.5	-- [g]	13.5	12	14
J_{eg}	-- [g]	-- [g]	10.5	-- [g]	10	-- [g]	9	8.5	3.5
J_{eh}[h]	-- [g]	-- [g]	-- [f]	-- [g]	-- [f]	-- [g]	1[h]	1[h]	2.5[h]
J_{fg}	-- [g]	2.5	2	-- [e]	1	-- [g]	-- [f]	-- [f]	3.3
J_{gh}	-- [g]	5	10	-- [g]	9.5	-- [g]	9	8.5	5
J_{gi}	-- [g]	5	5	5	5	-- [g]	-- [f]	-- [f]	2
J_{hi}	-- [g]	-- [e,r]	15.5	15.5	15	-- [g]	13.5	13.5	13

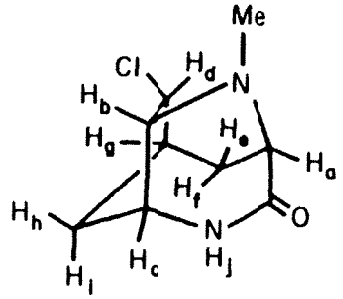
Table 8. Continued



45, R = Cbz, X = OH
48b, R = Me; X = OH
50, R = Cbz; X, H_d = O
51, R = Me; X = OSO_2Me
52a, R = Me; X = SePh



46, R = Cbz; X = OH
49b, R = Me; X = OH
54b, R = Me, X = Cl



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[a]90 MHz. [b]500 MHz. [c]Solvent, $CDCl_3$; reference, Me_4Si. [d]Solvent, D_2O; reference, $Me_3SiCH_2CH_2CO_2Na$. [e]Coupling not observed, $0 \leq J < 2$ Hz. [f]Coupling not observed, $0 \leq J < 1$ Hz. [g]Potential coupling constants, the values of which could not be ascertained due to incomplete resolution of the signals for the corresponding protons. [h]Four-bond coupling. [i]Not applicable. [j]δ 1.4-2.5 (m, H_e, H_f, H_i), 3.38 (br, OH). [k]δ 2.4-2.9 (m, H_e). [l]δ 2.2-2.7 (m, H_e, H_h), 3.04 (s, SCH_3). [m]A coupling to H_d of roughly 2 Hz was noted in the 90 MHz ^1H NMR spectrum of 52a, but was not observed in the 500 MHz spectrum. The origin of this coupling remains uncertain,

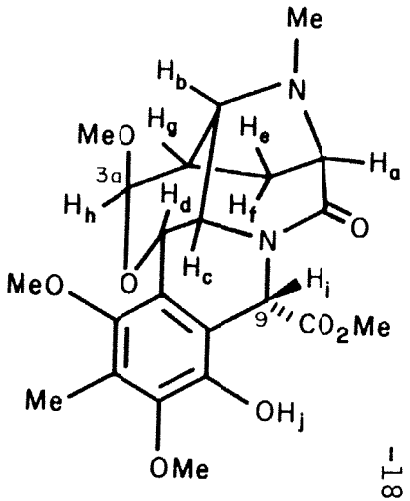
Table 8. Continued

but decoupling studies at 90 MHz suggest that it may involve H_h. [n] 1.4-2.7 (m, H_e, H_f, H_h, H_i). [o]This signal is obscured by the major coproduct, 56. [p]H_j is exchanged with the D_2O solvent. [q]Long range coupling J_{aj} and J_{ab} of 0.5-1.0 Hz are also noted. [r]This coupling is not observed due to the virtual coincidence of the resonances for H_h and H_i. [s] 7.29 (m, ortho- and para-aromatic-H), 7.52 (m, meta-aromatic-H).

Table 9. 500 MHz ^{1}H NMR Spectral Data for Pentacyclic Phenol 93.[a]

Proton[c]	Chemical Shift (δ)	Coupling Constant[b] (Hz) With H_a	H_b	H_c	H_d	H_e	H_f	H_g
H_a	3.49	--	--	1[e]	--	7	1	--
H_b [d]	3.57	--	--	4.5	--	--	--	6
H_c	3.61	1[e]	4.5	--	1	--	--	0.8
H_d [d]	5.05	--	--	1	--	--	--	--
H_e	2.49	7	--	--	--	--	12.5	12
H_f [d]	2.02	1	--	--	--	12.5	--	6.5
H_g [d]	2.59	--	6	0.8	--	12	6.5	--
H_h [d]	4.96	--	--	--	--	--	--	--
H_i [d]	5.57	--	--	--	--	--	--	--

[a] $CDCl_3$ solution. [b] Blank entries: $0 \leq J \leq 1$ Hz. [c] Other signals: δ 7.17 (broad, H_j), 3.83 (s, OCH_3), 3.76 (s, OCH_3), 3.70 (s, OCH_3), 3.57 (s, 3a-OCH_3), 2.55 (s, NCH_3), 2.23 (aromatic-CH_3, an unexplained splitting of ~0.7 Hz is present in this signal). [d] Small (≤ 1 Hz), unassigned coupling(s) is (are) present, in addition to those tabulated. [e] Tentative assignment.



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VI. References and Notes

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(69) It was noted that the crude ozonolysis product was enriched in isomer 88a relative to 88b, whereas the mixture obtained after chromatography either contained roughly equal amounts of 88a and 88b, or was slightly enriched in 88b (^{1}H NMR). Equilibration between the two isomers may be occurring during chromatography. The assignment

of the signals for the individual isomers in the ^{1}H NMR spectra of the mixture 88a,b was based upon the relative chemical shifts of the carbinol (13b) protons. According to literature precedent,[70,71] the lower field carbinol proton resonance was assigned to the isomer possessing that proton in the equatorial orientation (ie, 88b).

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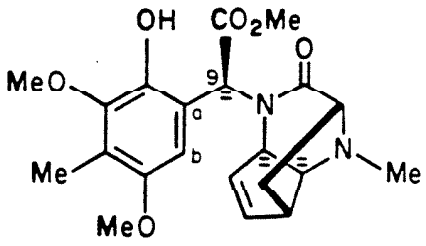
(83) ^{1}H NMR revealed that the major isomer of recovered 81 was the minor isomer of starting 81.

(84) The carbonyl carbon resonances did not appear under the conditions in which this spectra was obtained.

(85) This splitting is most likely an example of virtual coupling. See reference 28; Chapter 2-3, pp. 147-9.

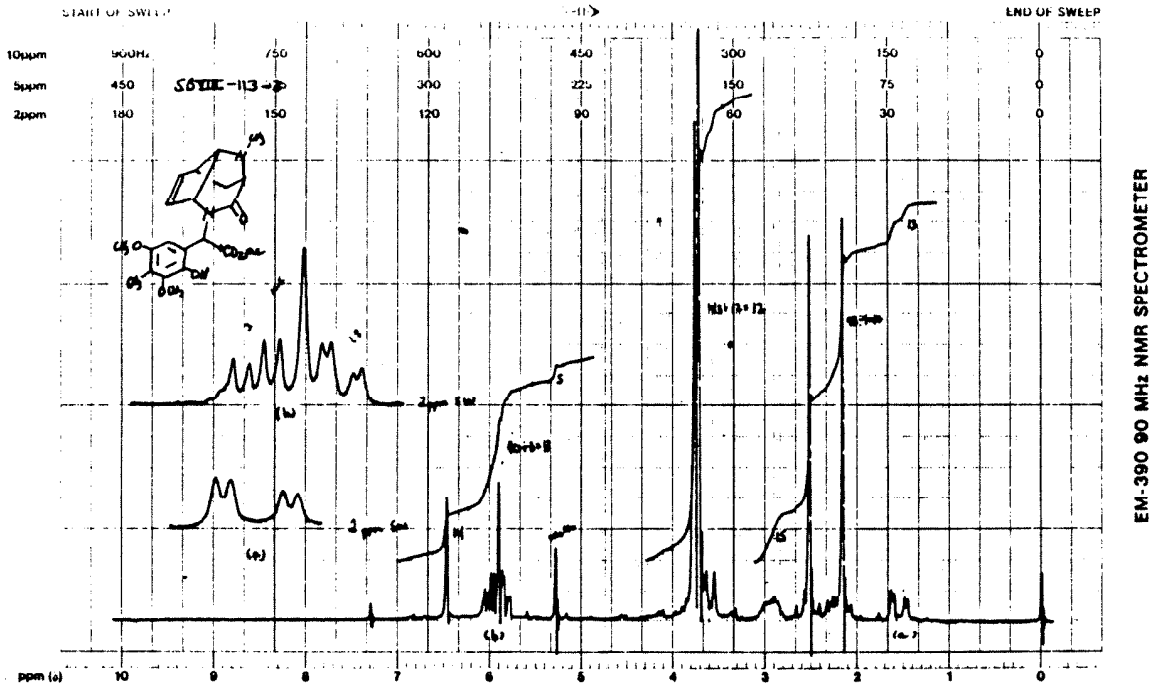
APPENDIX I

IR and NMR Spectral Catalog

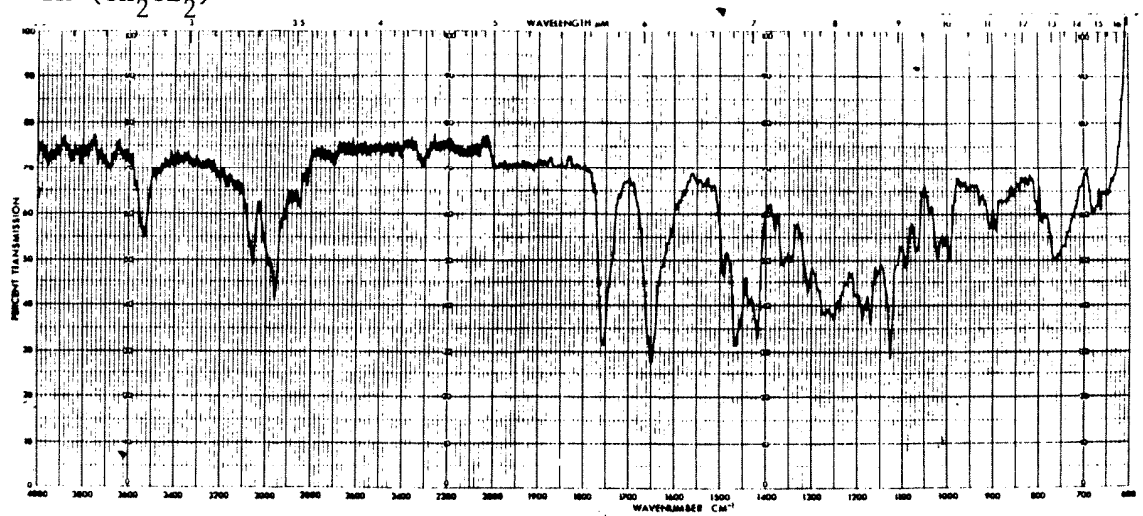


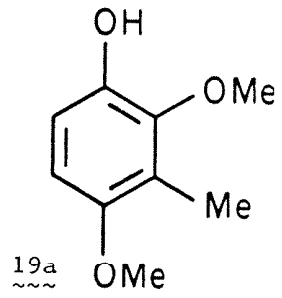
18

^{1}H NMR ($CDCl_3$)



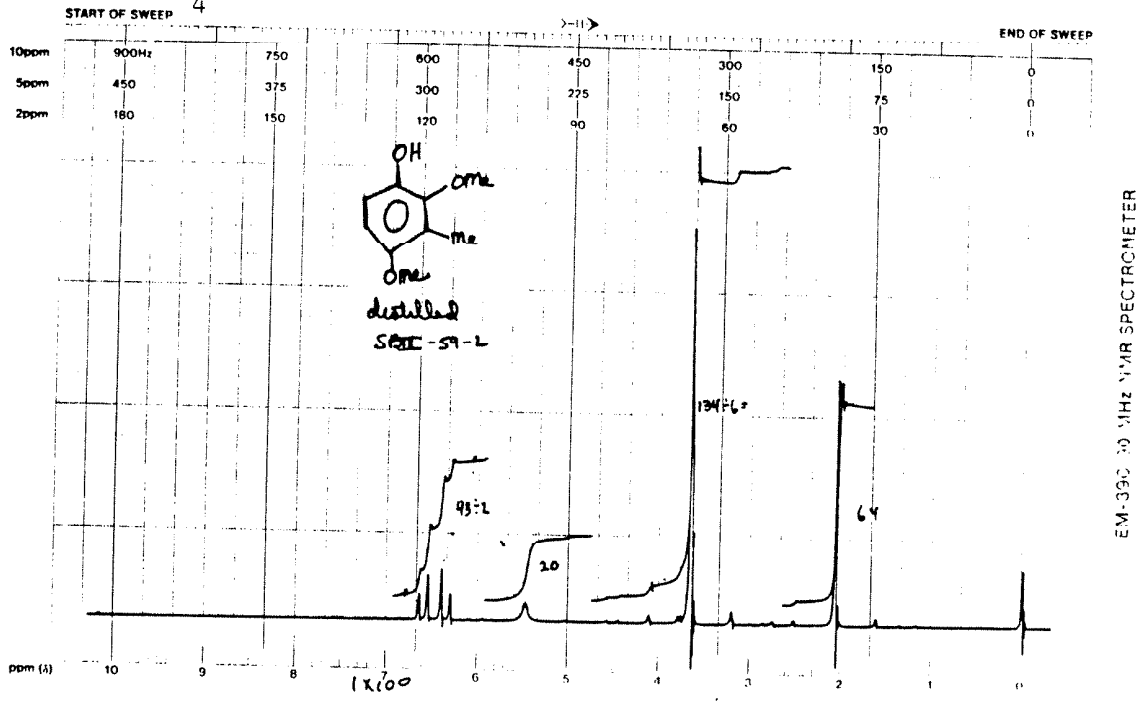
IR (CH_2Cl_2)



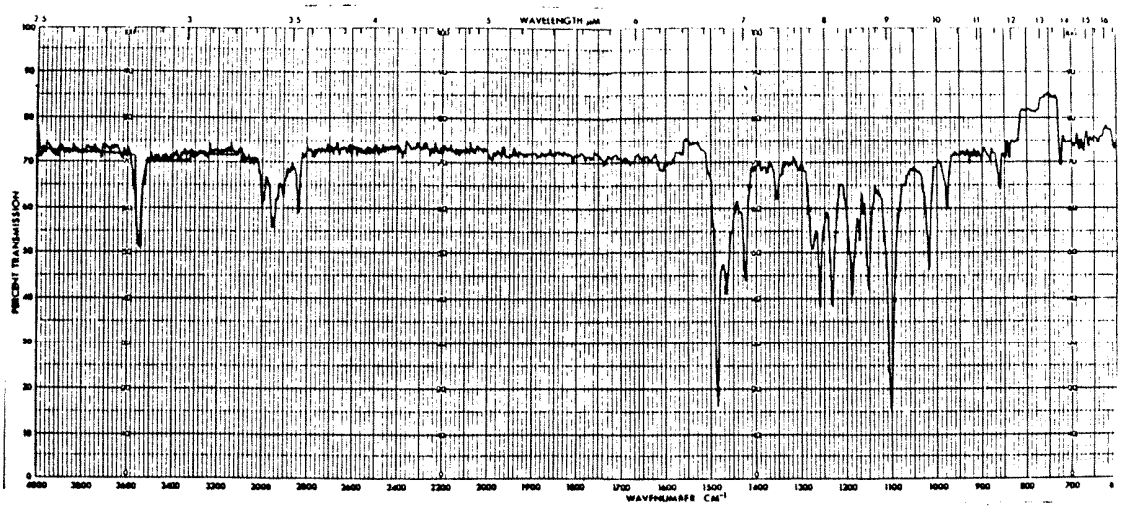


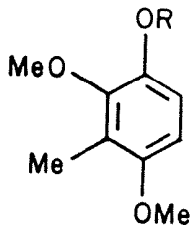
19a

^{1}H NMR (CCl_4)



IR (CCl_4)

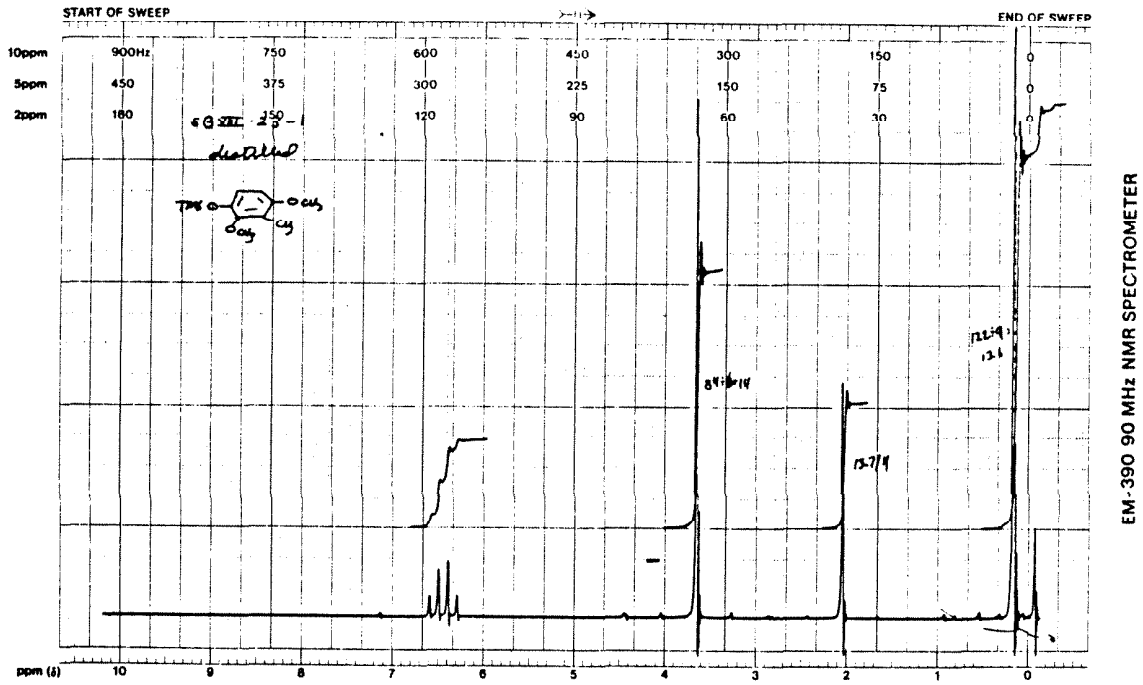




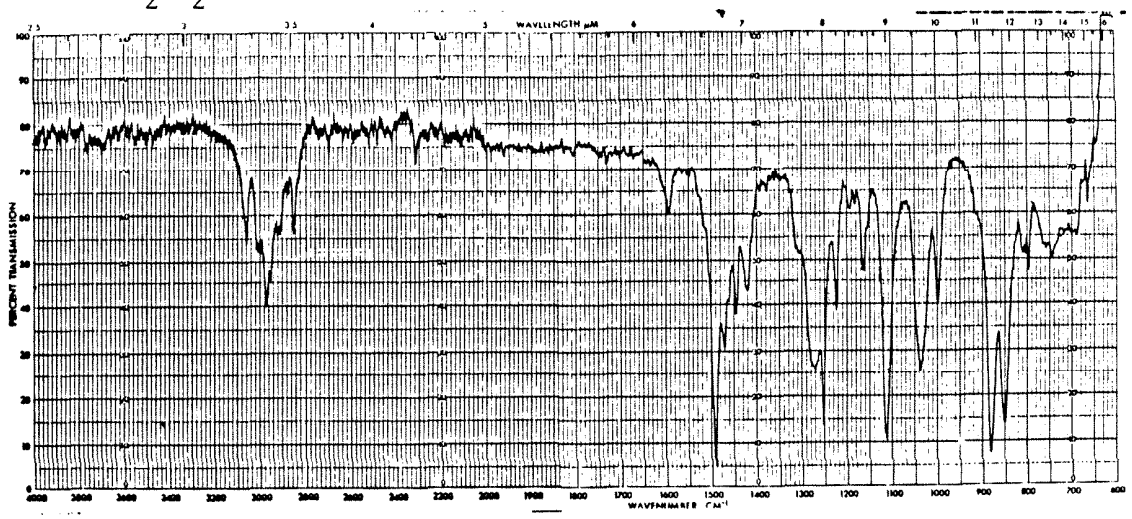
19b

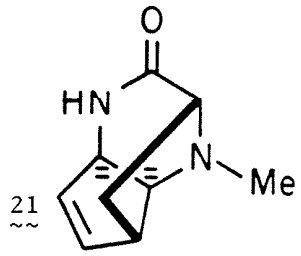
R = Me_3Si-

^1H NMR ($CDCl_3$)



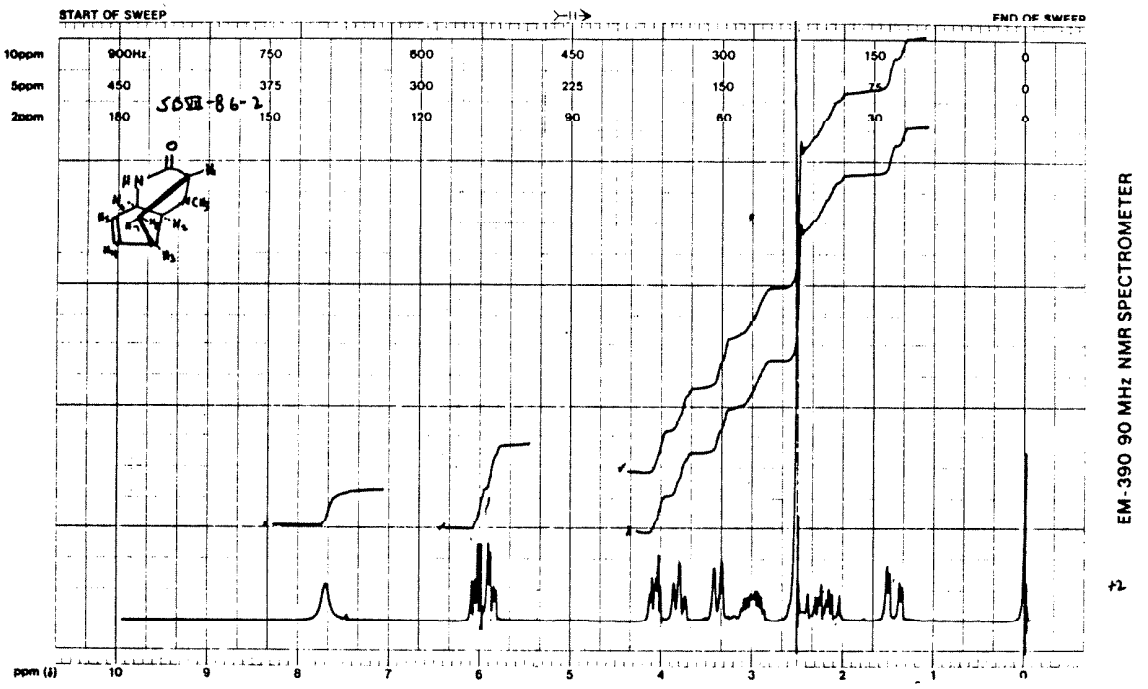
1R (CH_2Cl_2)



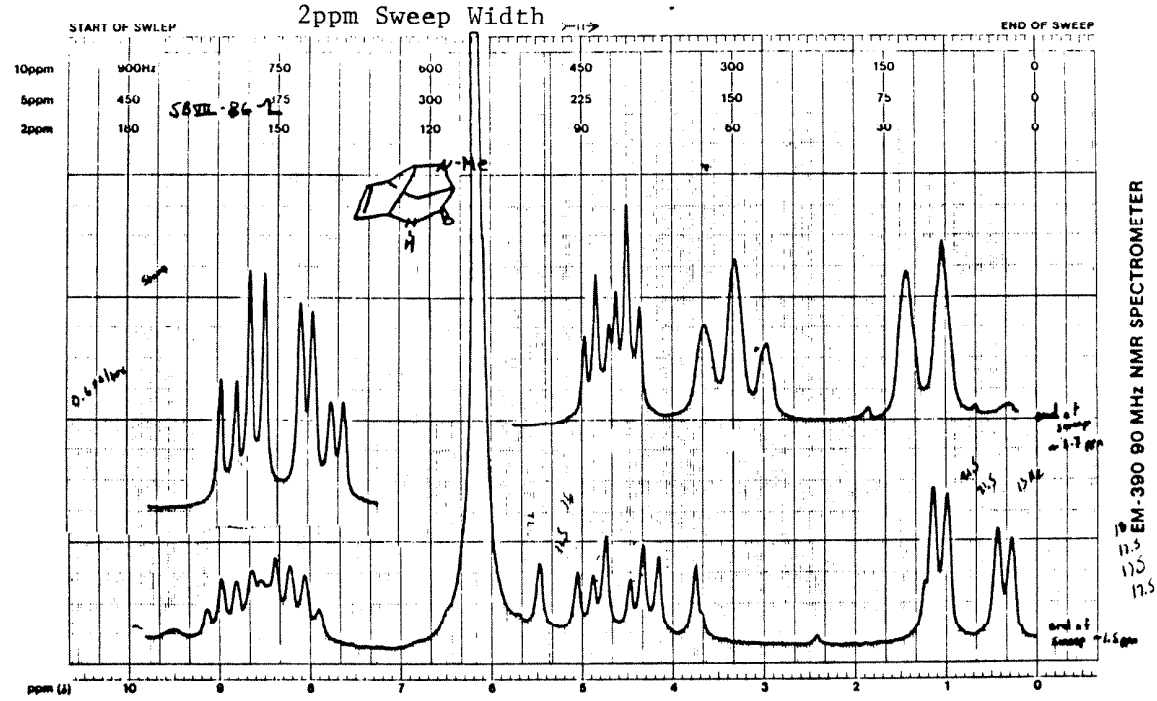


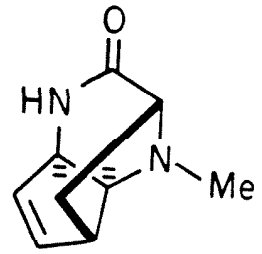
21

^{1}H NMR ($CDCl_3$)



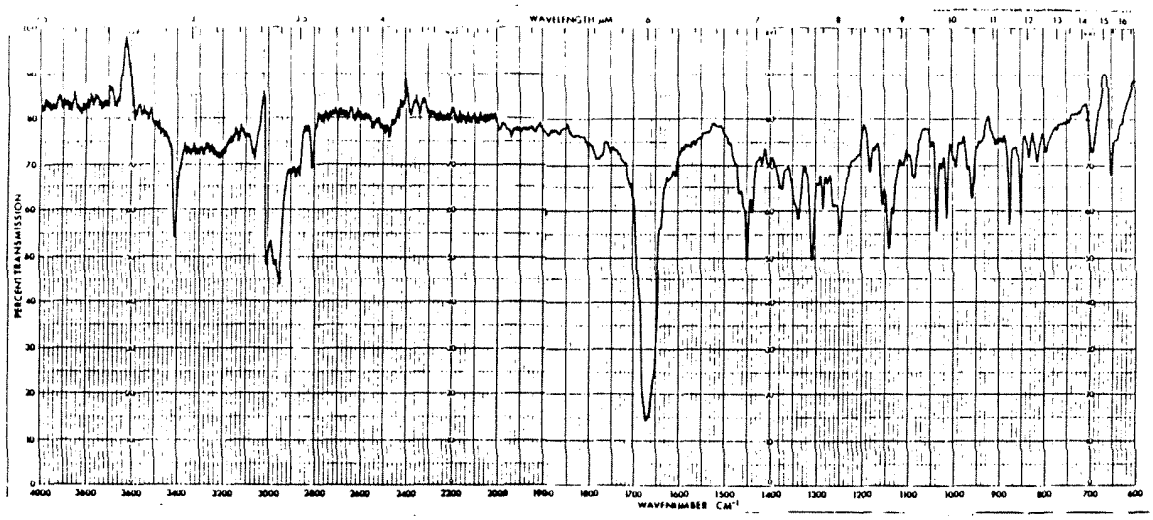
2ppm Sweep Width



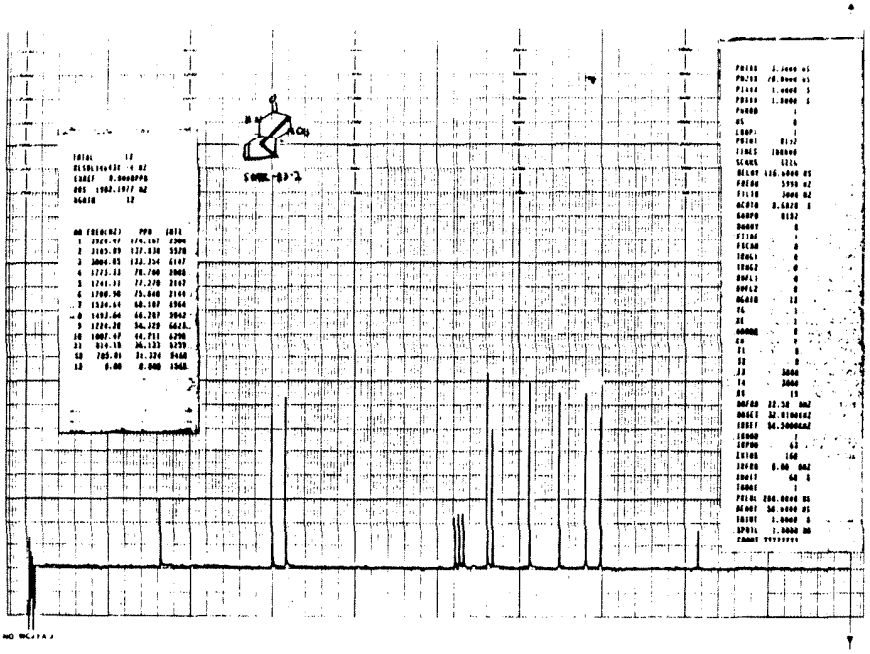


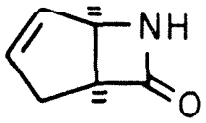
21

1R ($CHCl_3$)



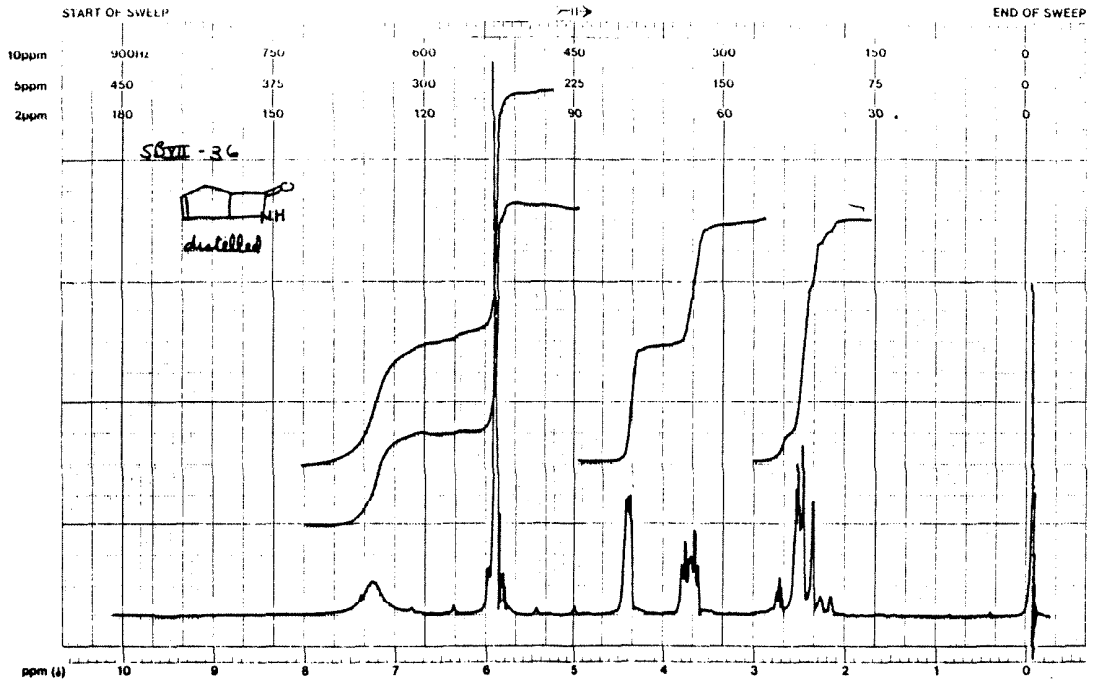
^{13}C NMR ($CDCl_3$)



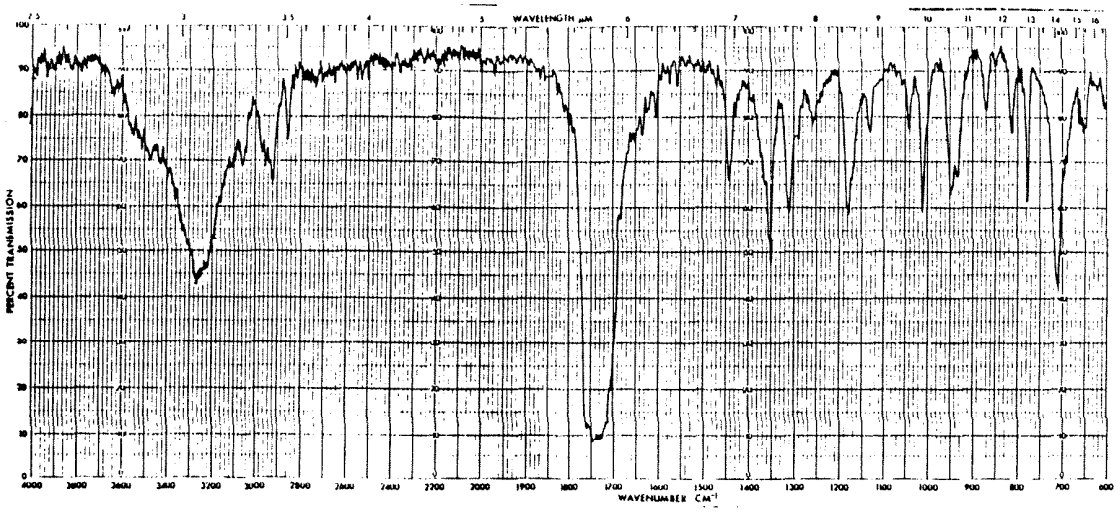


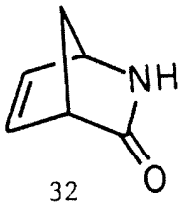
31

^{1}H NMR ($CDCl_3$)



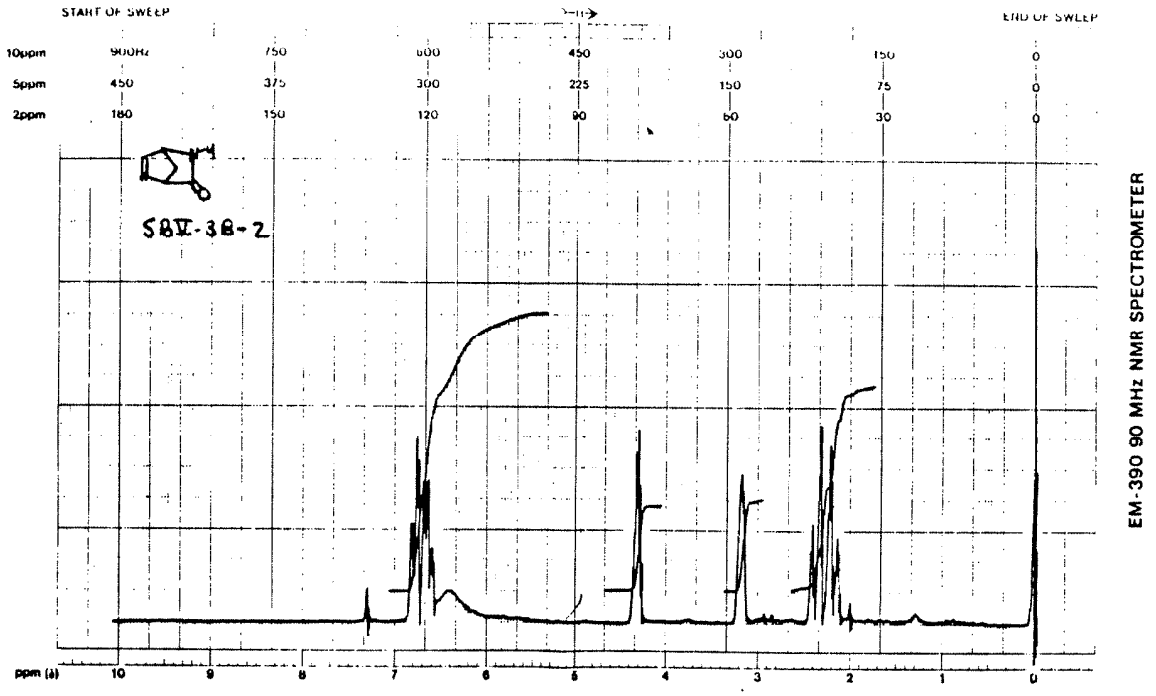
IR (neat)



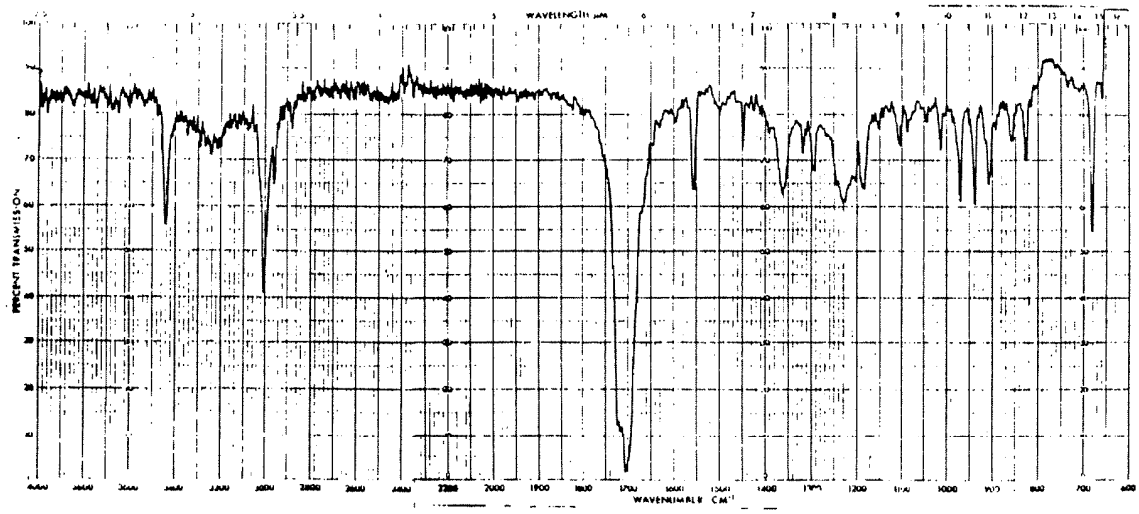


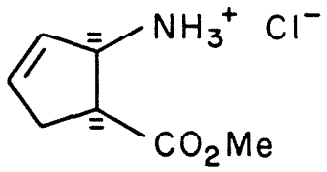
32

^{1}H NMR ($CDCl_3$)



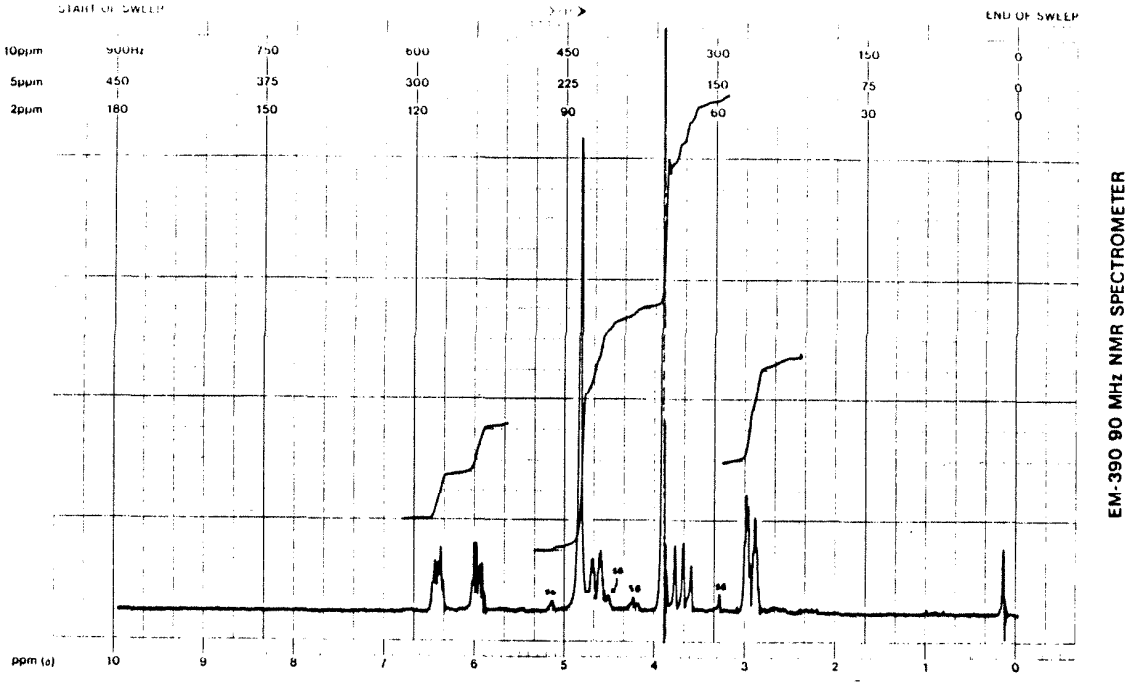
IR ($CHCl_3$)



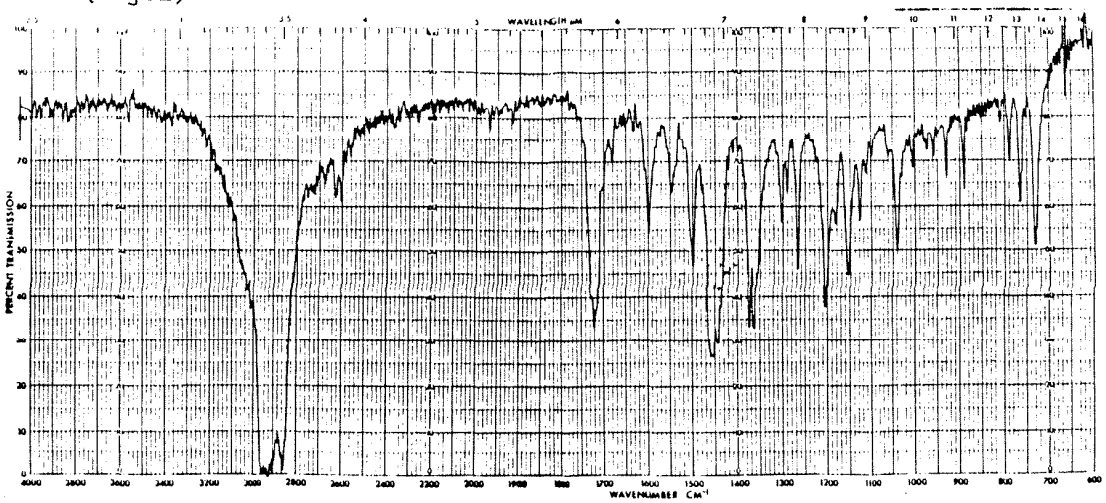


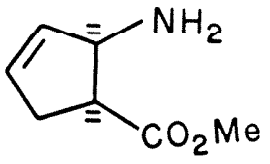
33

^{1}H NMR (D_2O)



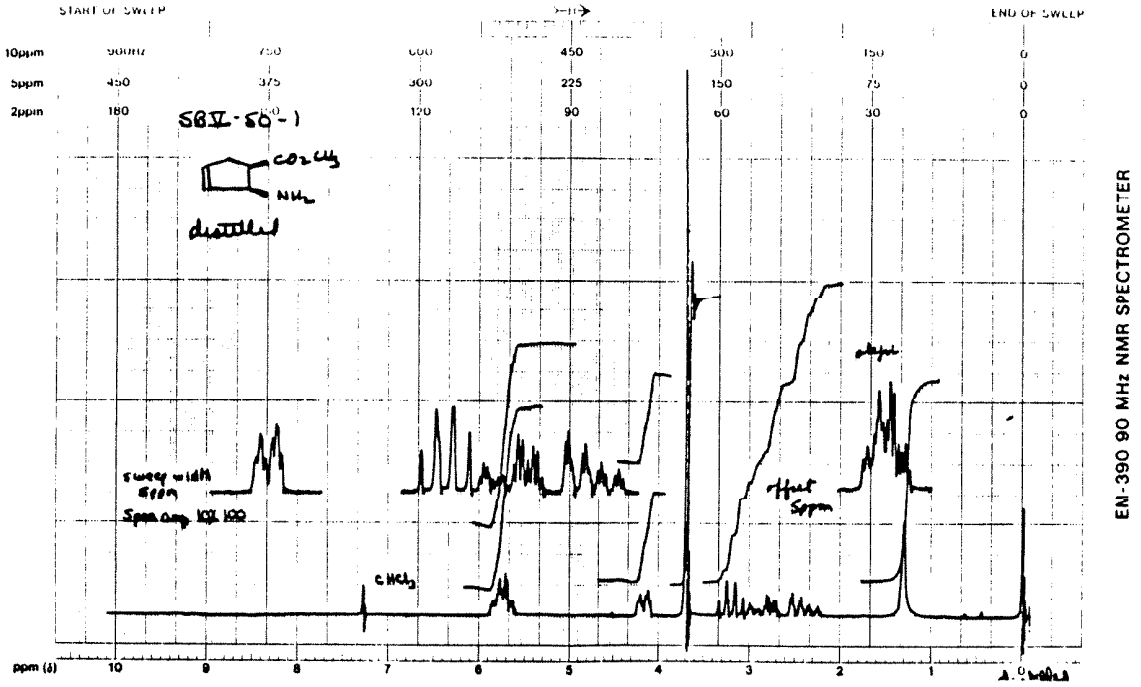
IR (Nujol)



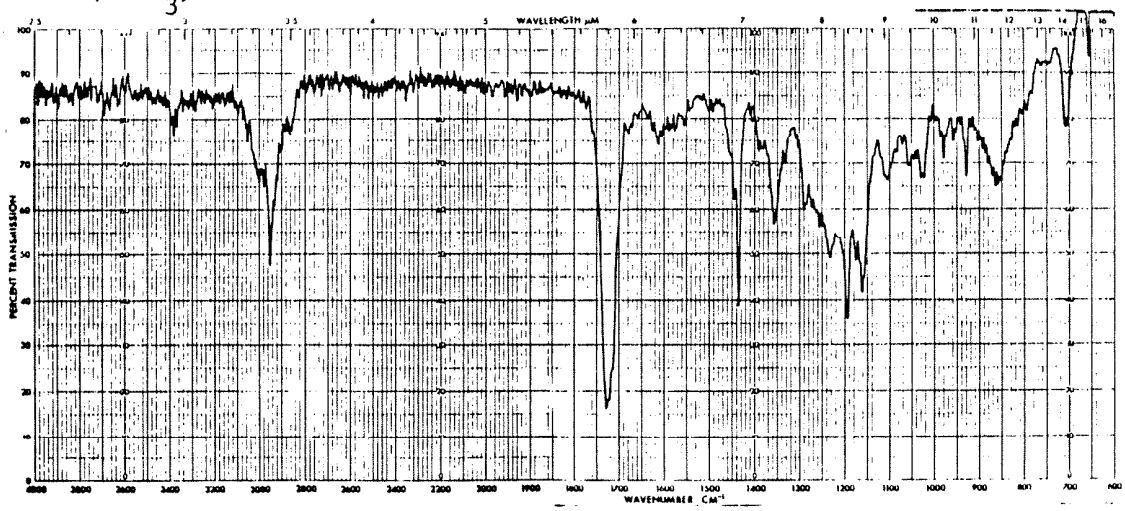


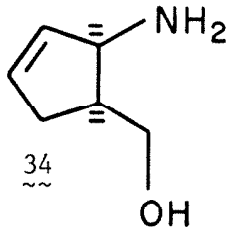
Free base from 33
Bulb-to-bulb distilled (85-90°C, < 1mm)

^{1}H NMR ($CDCl_3$)



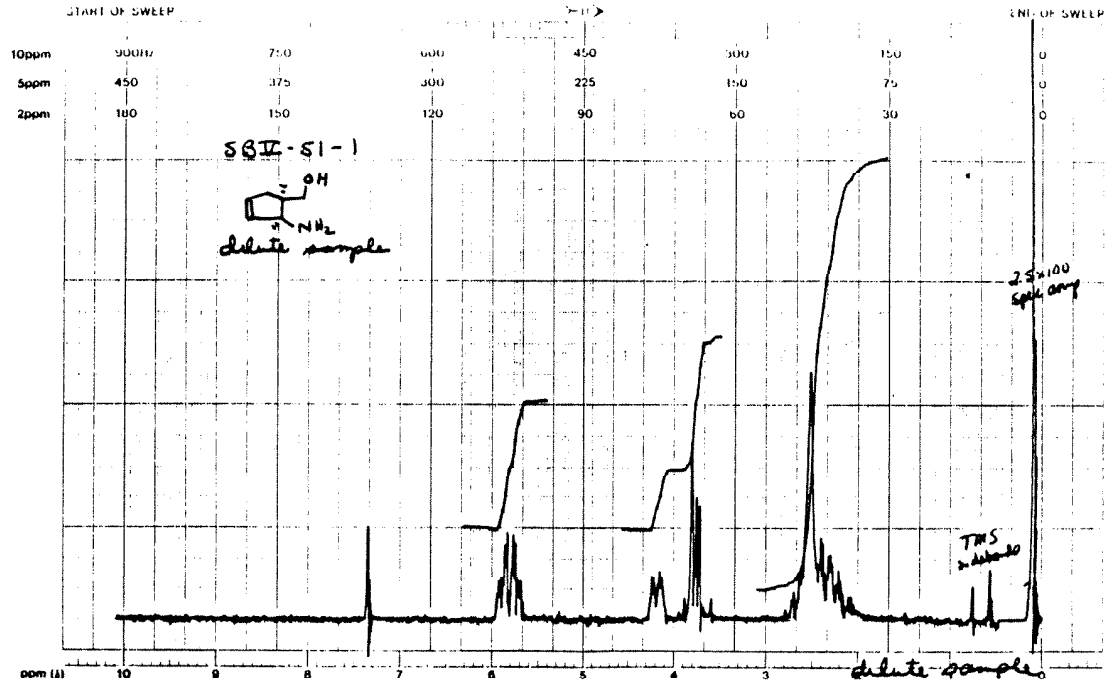
IR ($CHCl_3$)



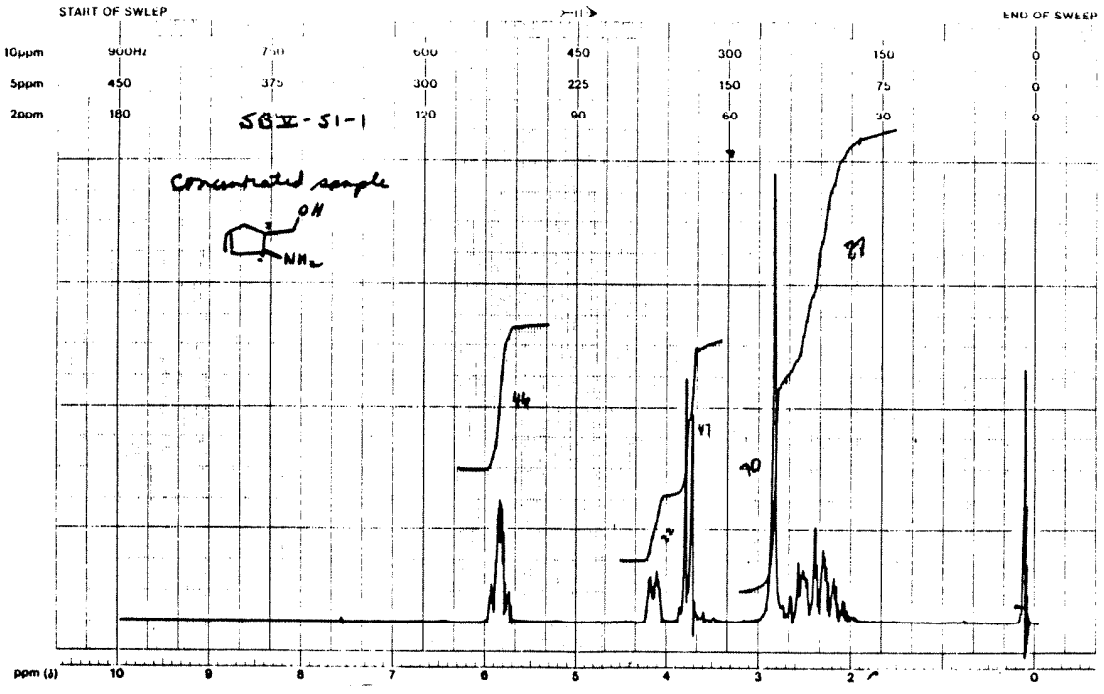


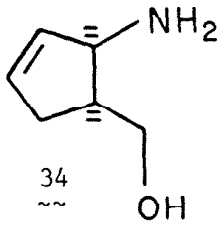
34

^{1}H NMR ($CDCl_3$) Dilute, Spec. Amp. = 2.5 x 1000



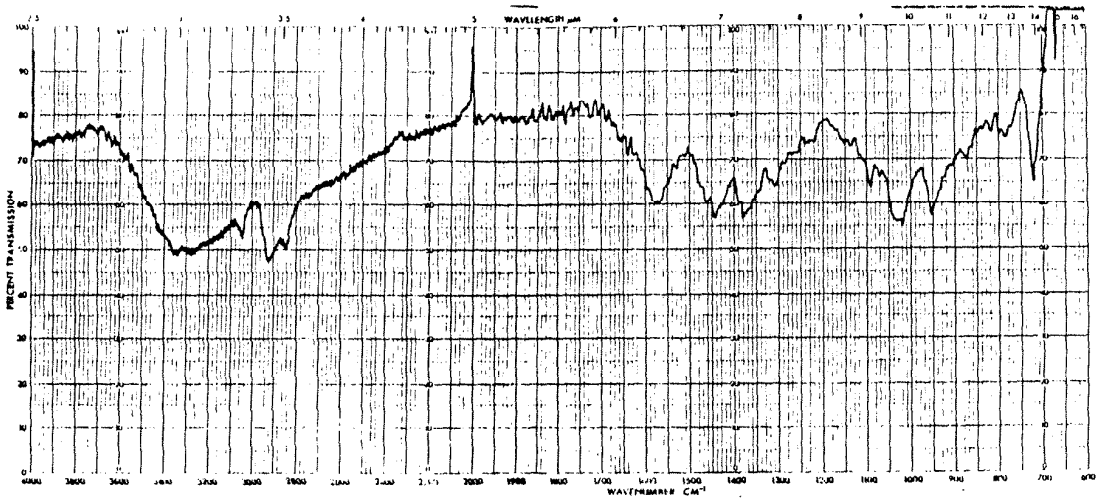
^{1}H NMR ($CDCl_3$) Concentrated, Spec. Amp. = 2 x 100





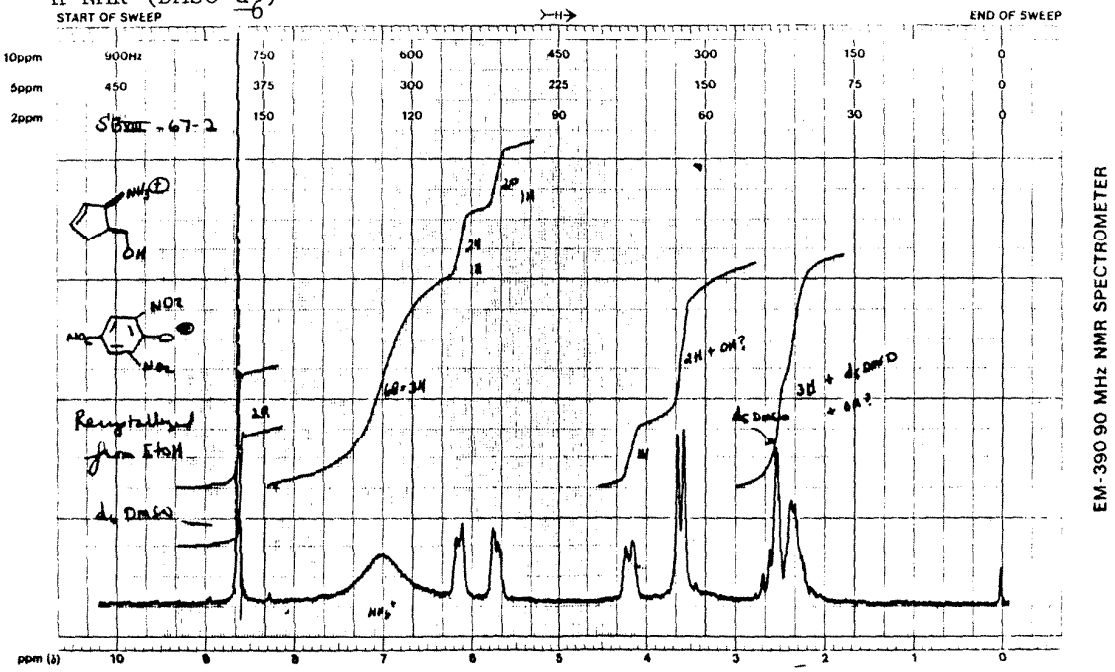
34

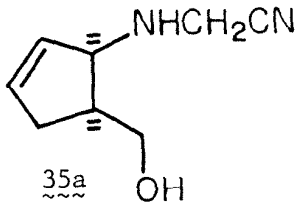
1R (neat)



Picrate Salt of 34

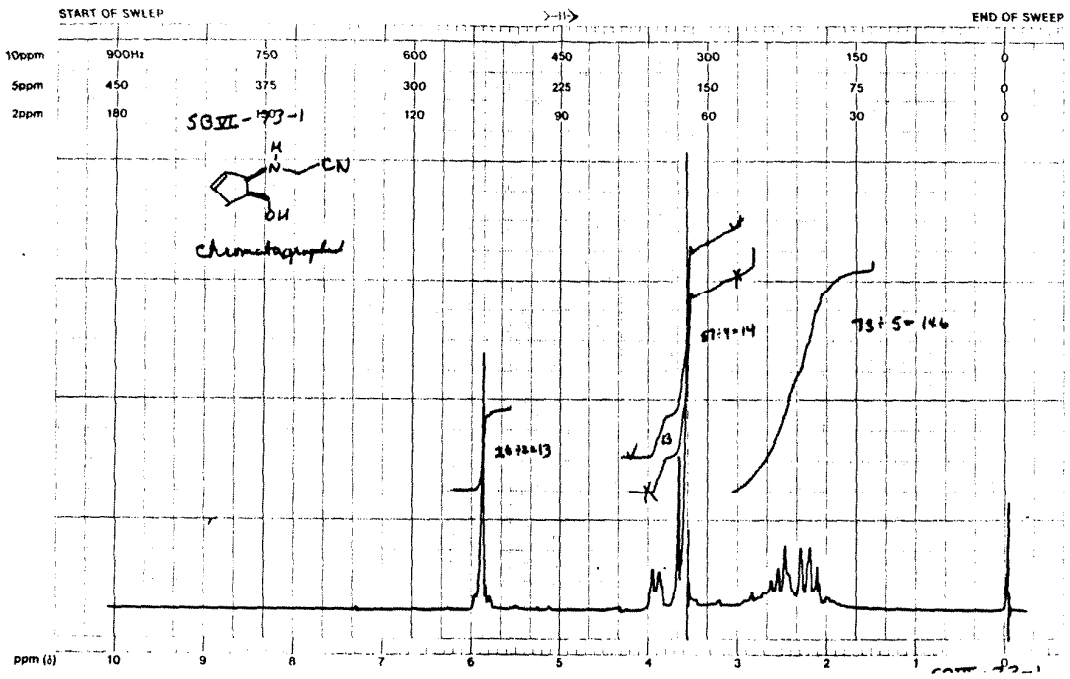
^{1}H NMR (DMSO-d_6)



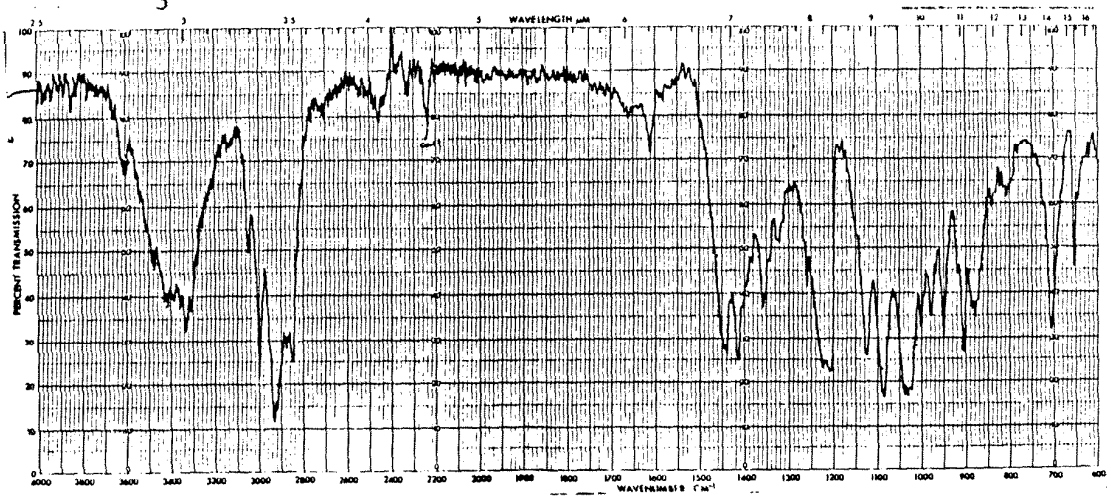


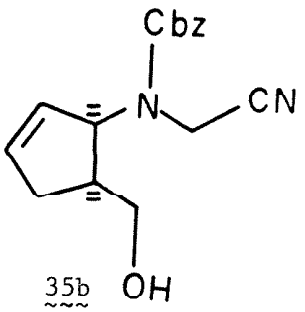
35a

^{1}H NMR ($CDCl_3$)



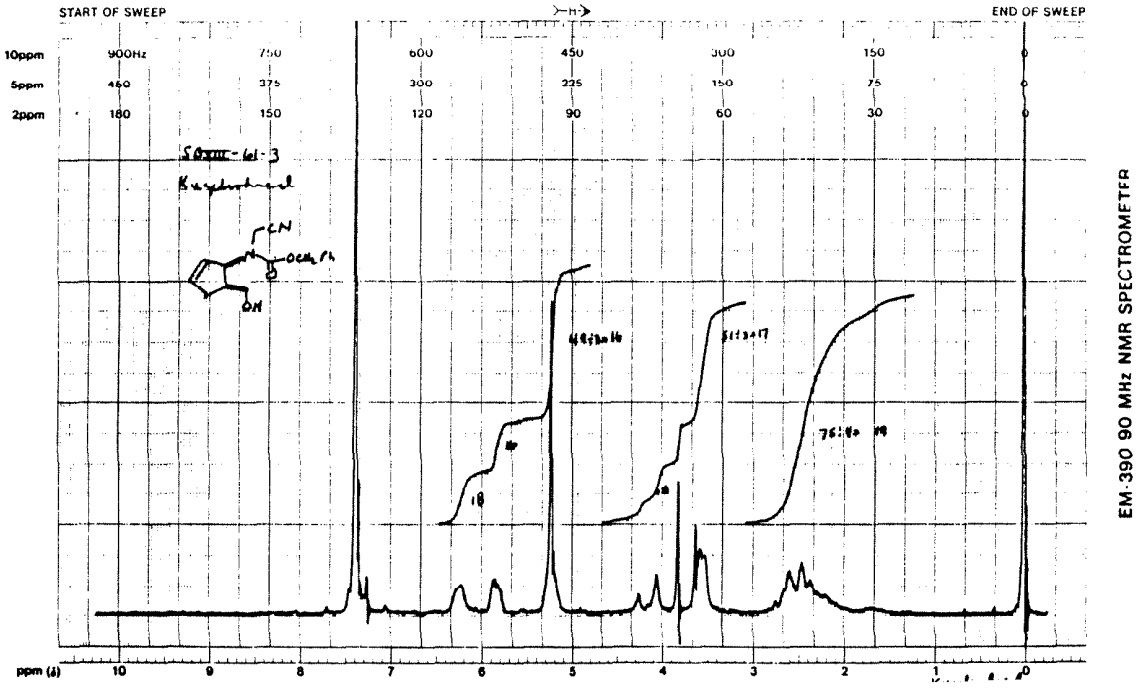
1R ($CHCl_3$)



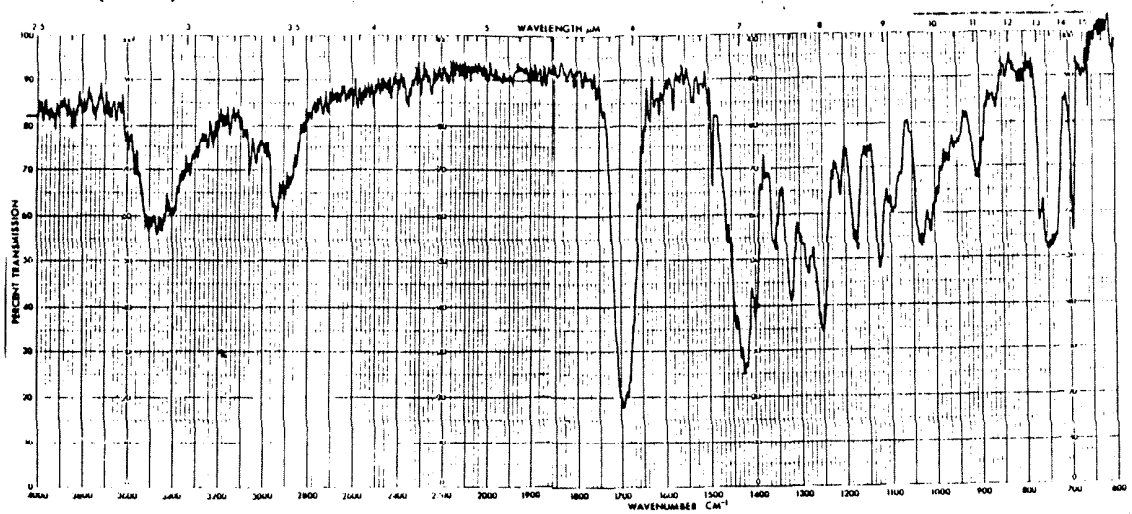


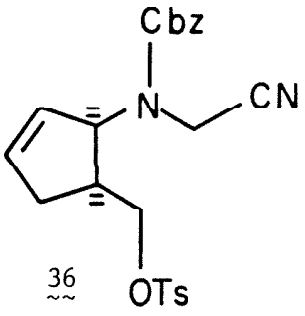
35b

^{1}H NMR ($CDCl_3$)



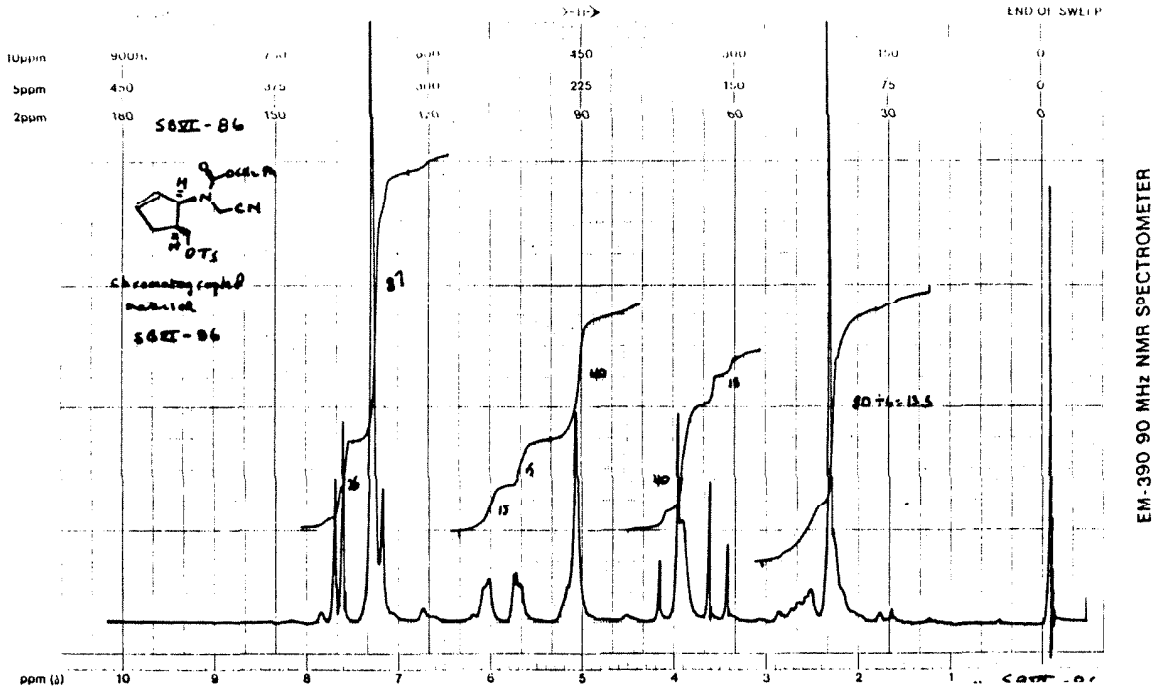
1R (neat)



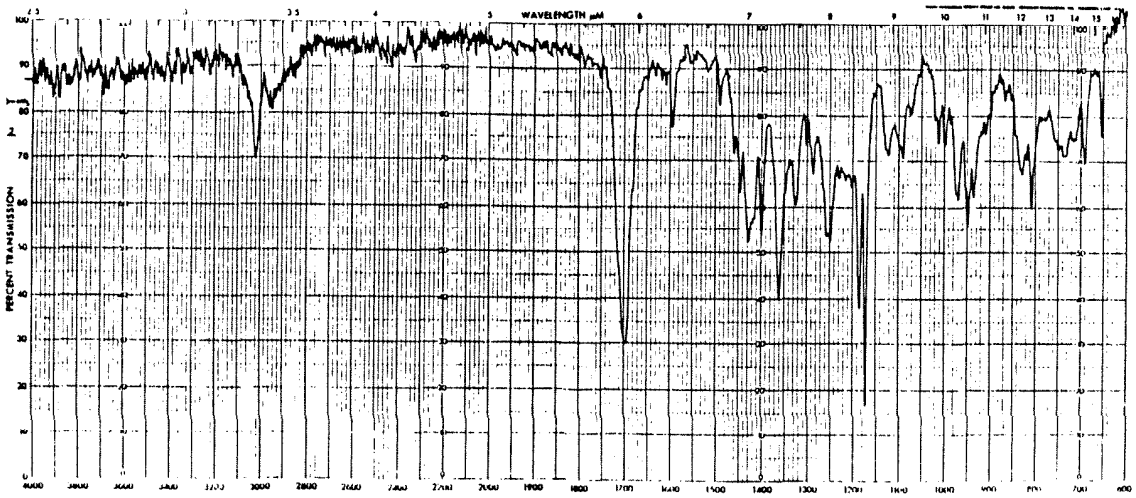


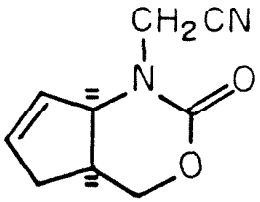
36

^{1}H NMR ($CDCl_3$)



IR ($CHCl_3$)





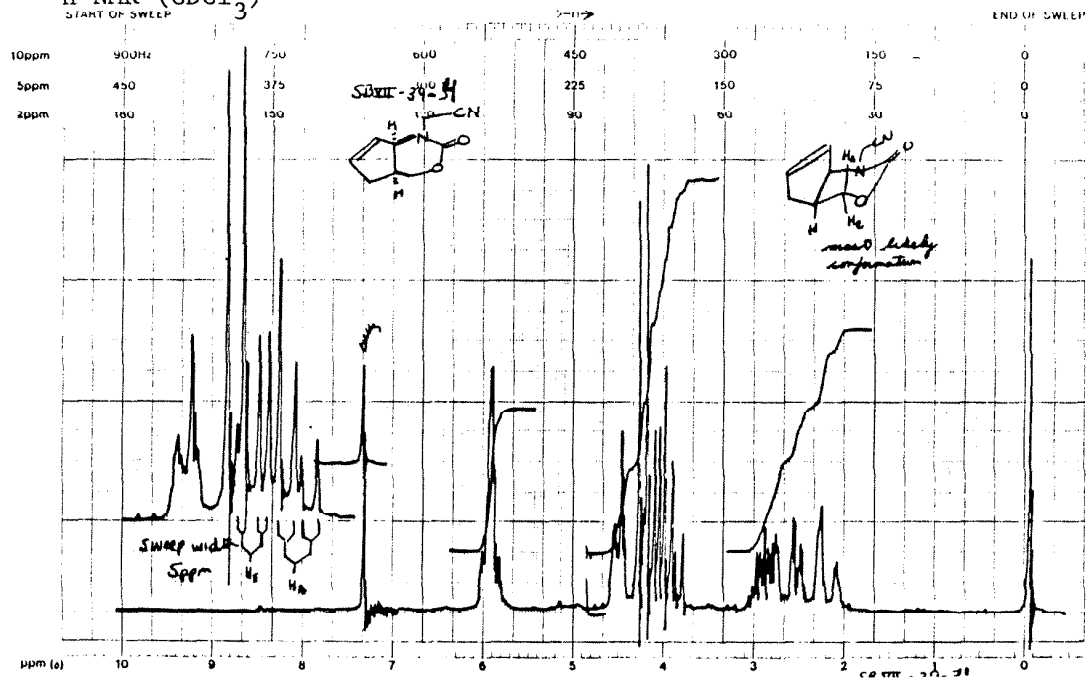
37b

colorless oil

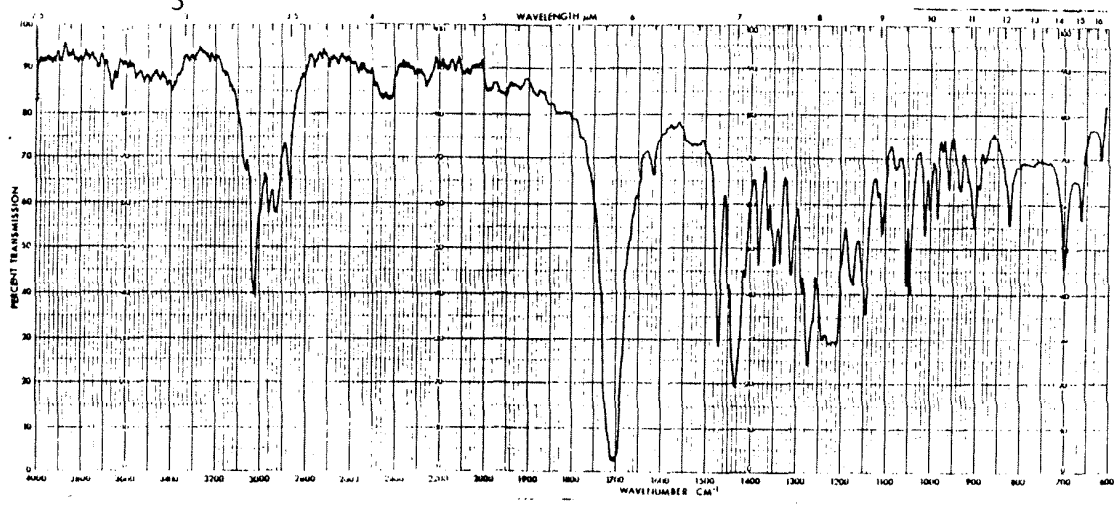
Exact Mass calcd. for $C_9H_{10}N_2O_2$: 178.0742

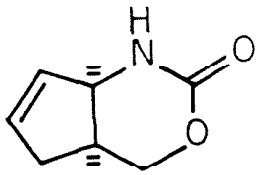
found : 178.0741

^1H NMR ($CDCl_3$)



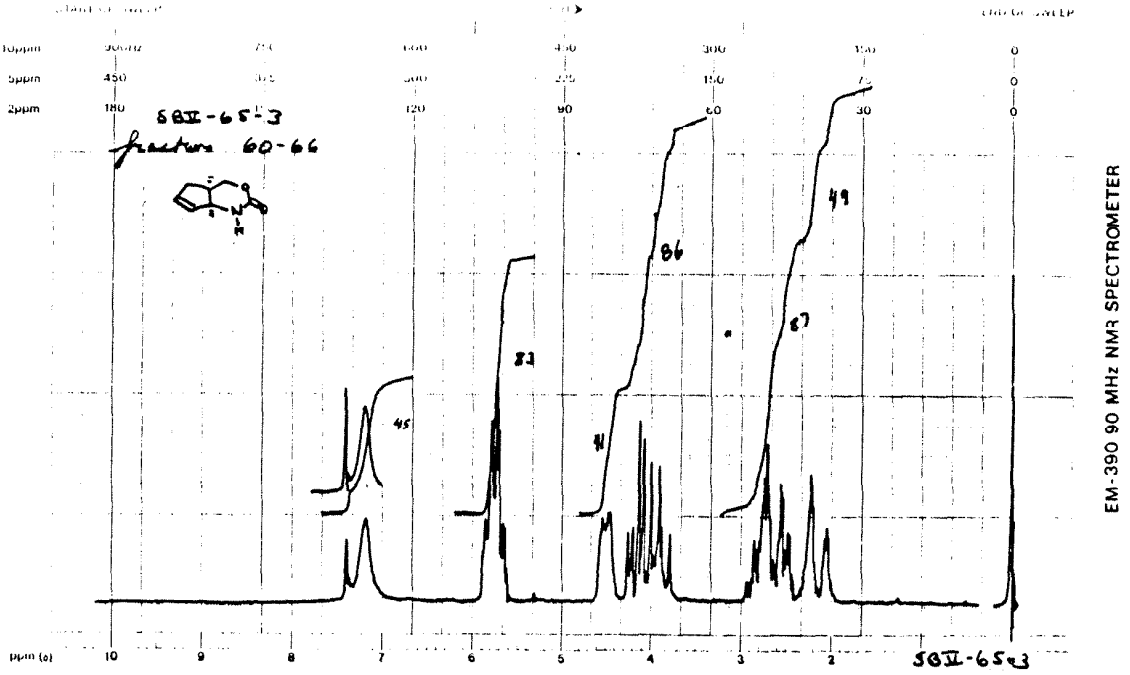
1R ($CHCl_3$)



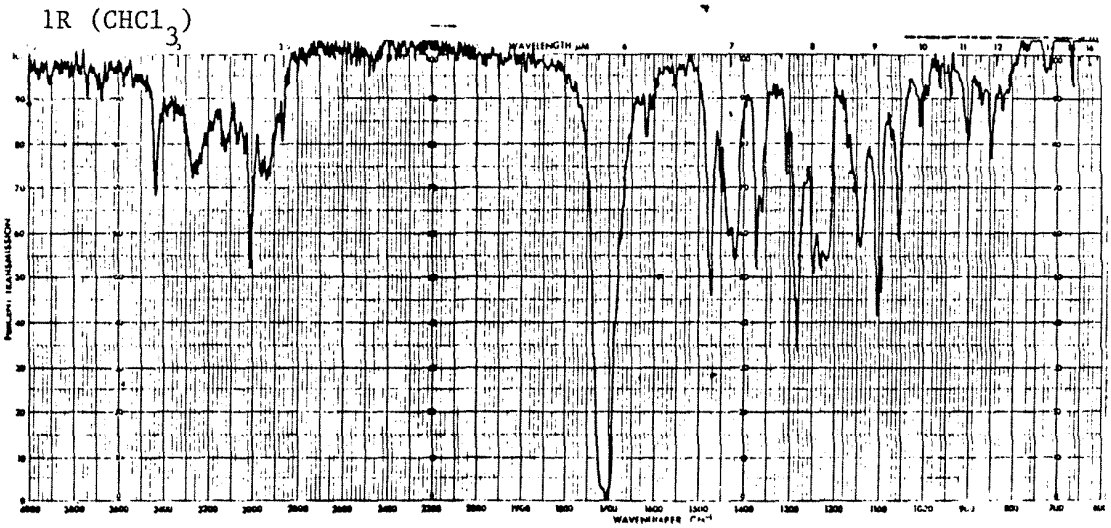


37b
liquid

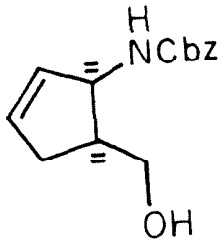
^{1}H NMR ($CDCl_3$)



IR ($CHCl_3$)

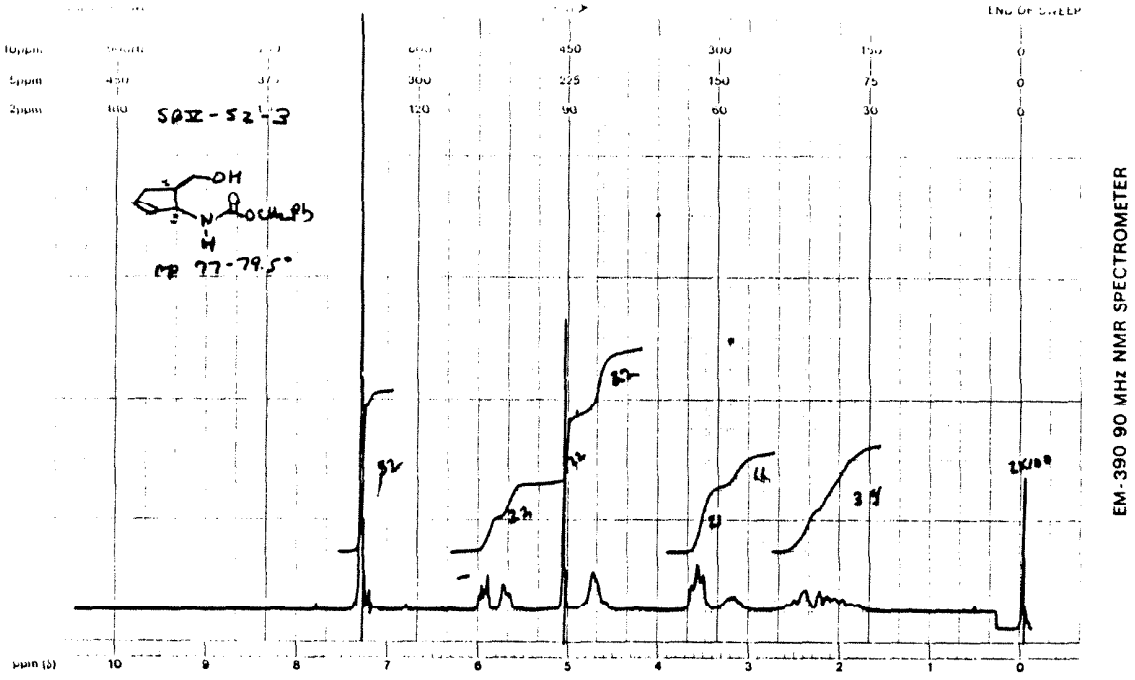


White solid, mp 77-79.5°C
Exact Mass calcd. for $C_{14}H_{17}NO_3$: 247.121
Found : 247.123

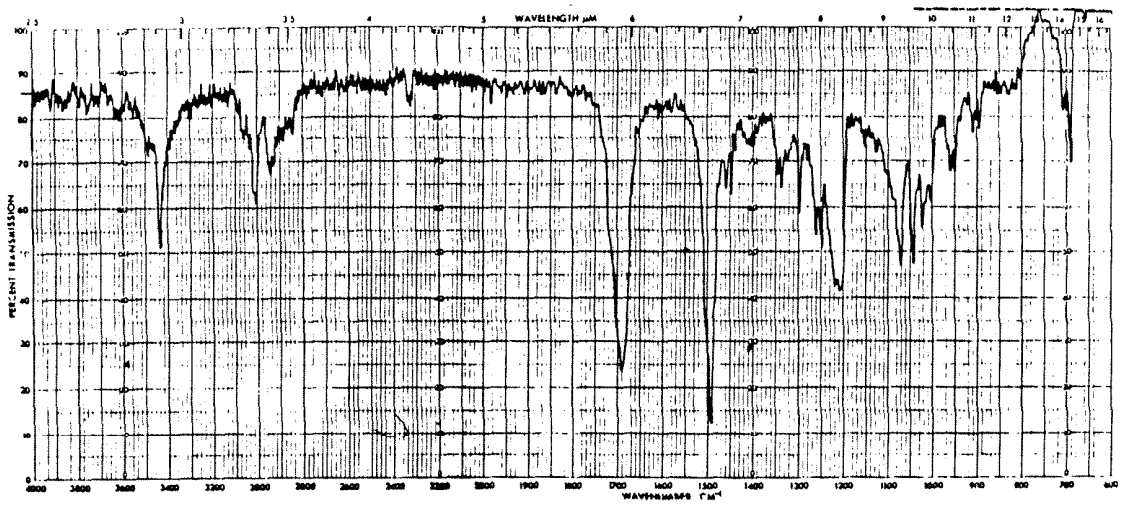


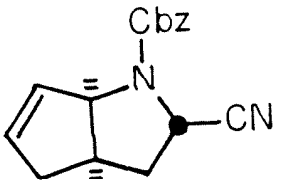
N
pp. ~23,24

^{1}H NMR ($CDCl_3$)



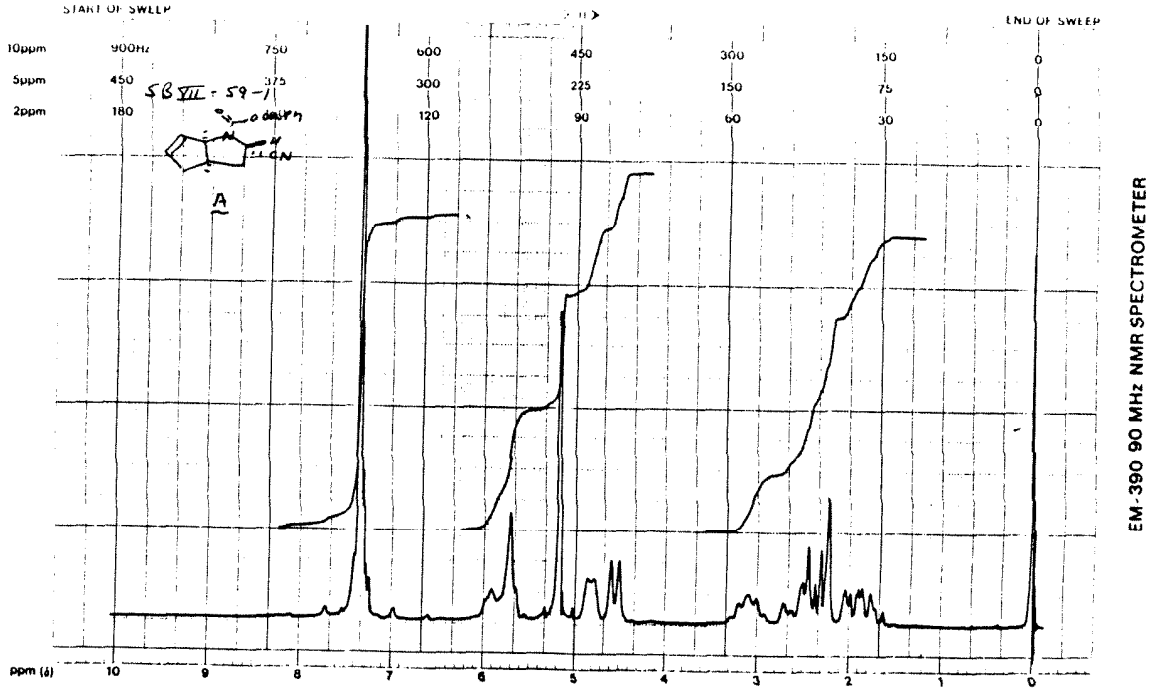
IR ($CHCl_3$)



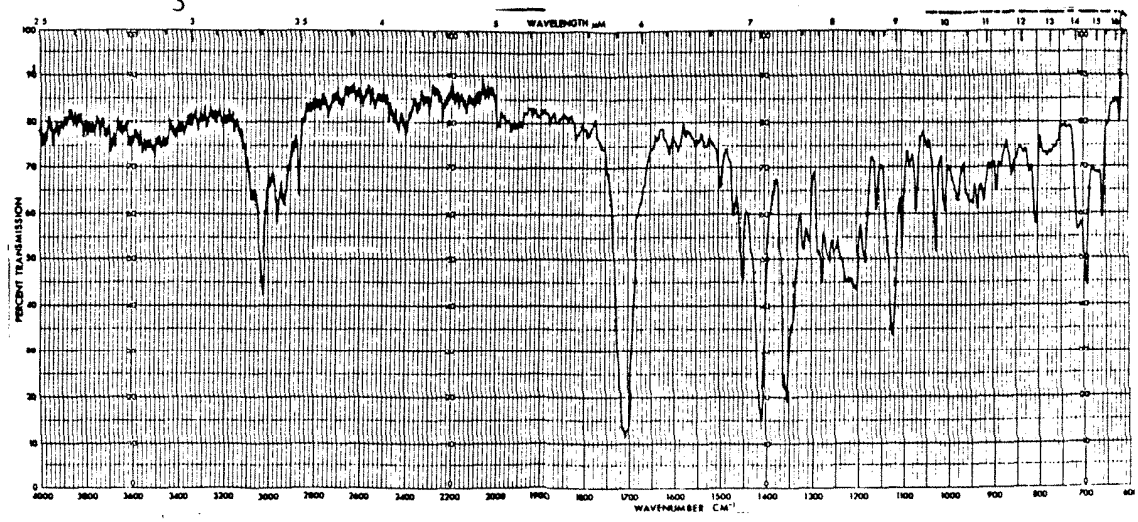


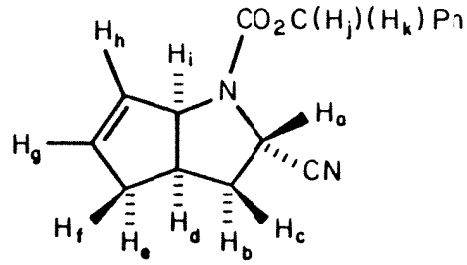
38

^{1}H NMR ($CDCl_3$)



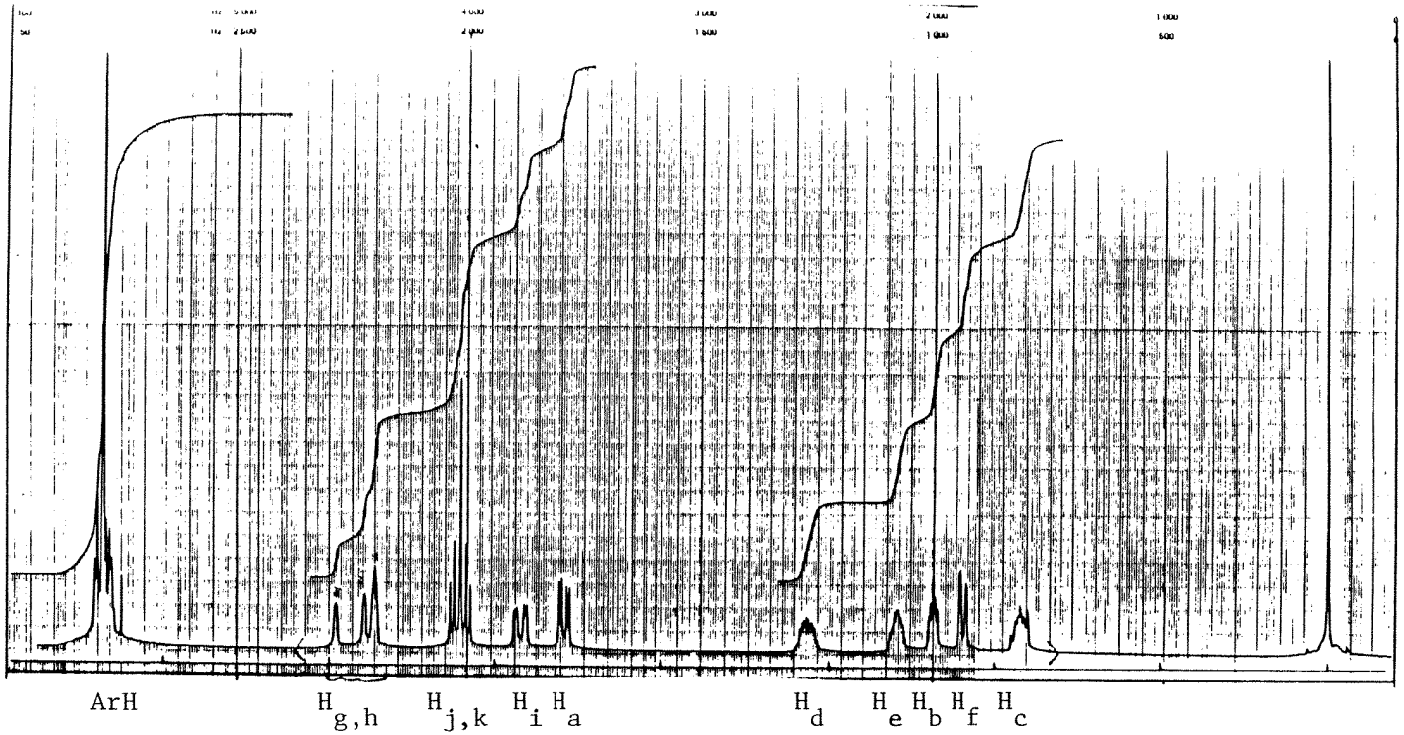
1R ($CHCl_3$)



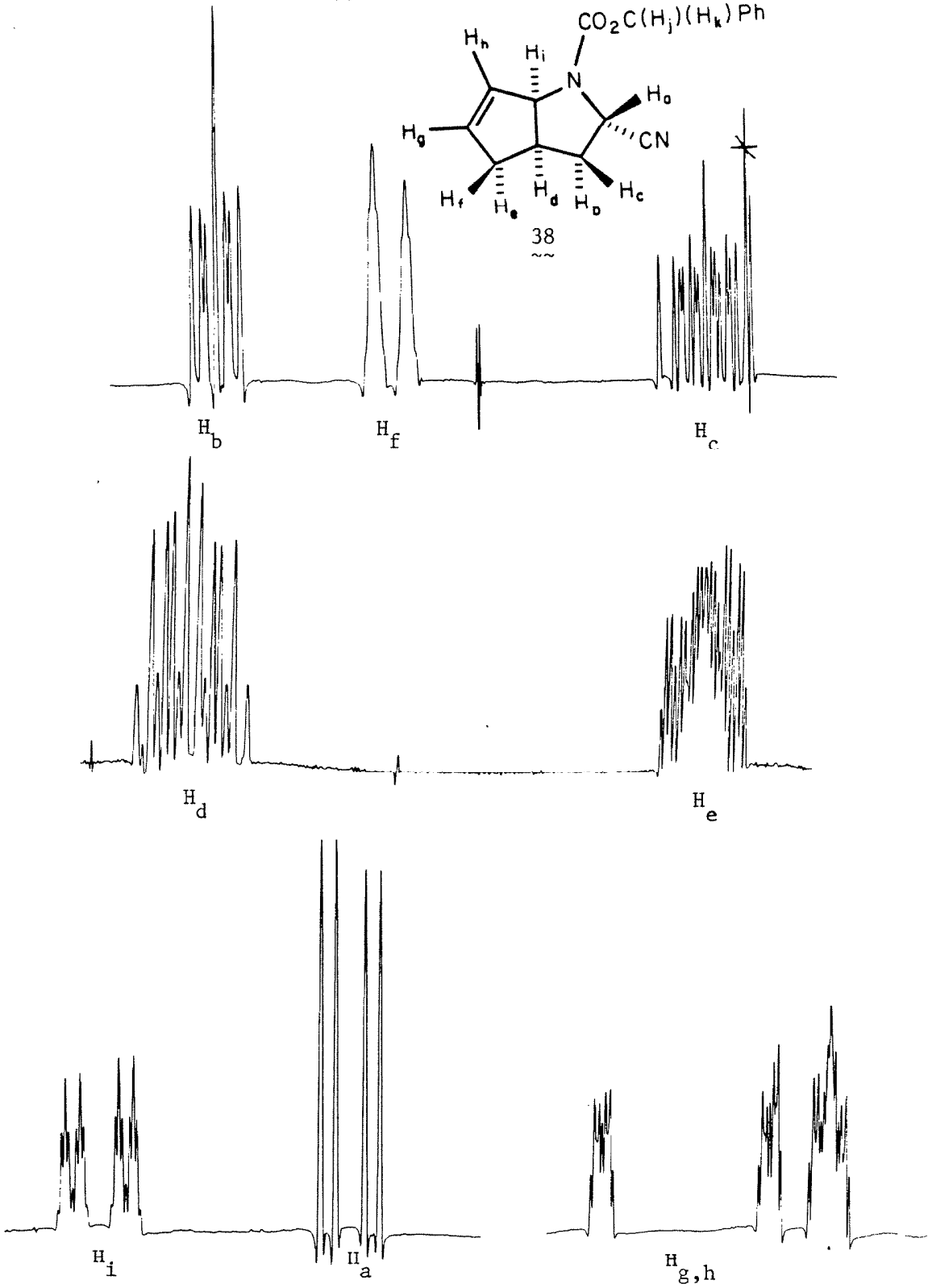


38

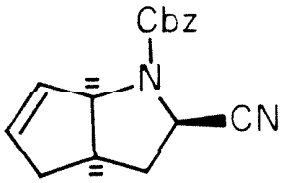
500 MHz ^{1}H NMR Spectrum of 38 ($CDCl_3$).



500 MHz ^{1}H NMR Spectrum of 38: Expansions.

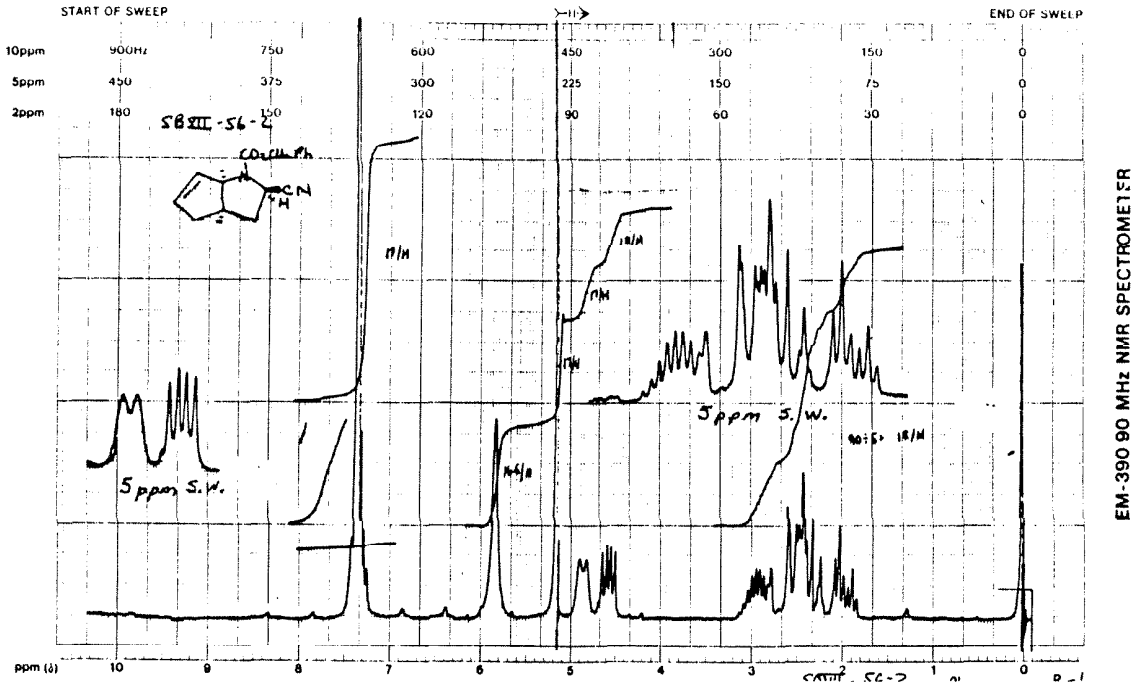


38

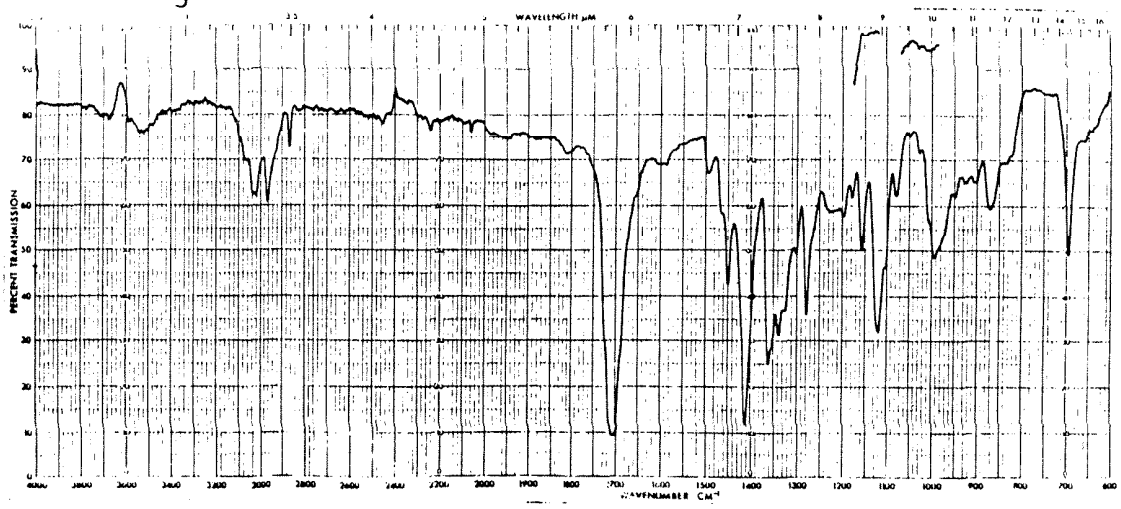


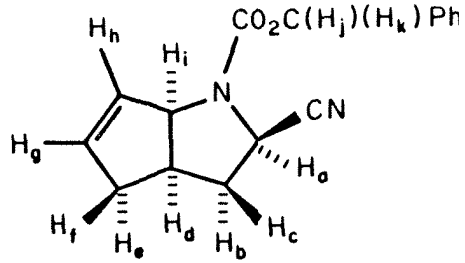
39

^{1}H NMR ($CDCl_3$)



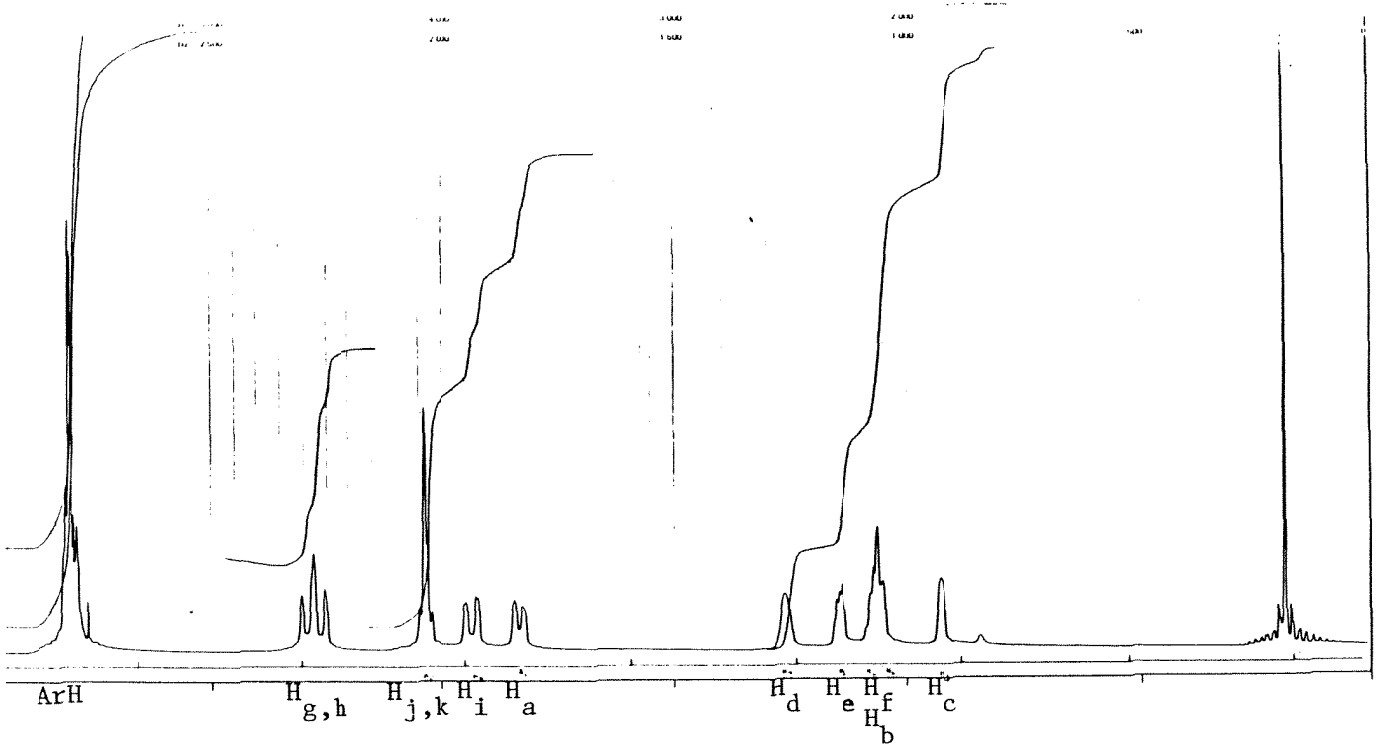
IR ($CHCl_3$)



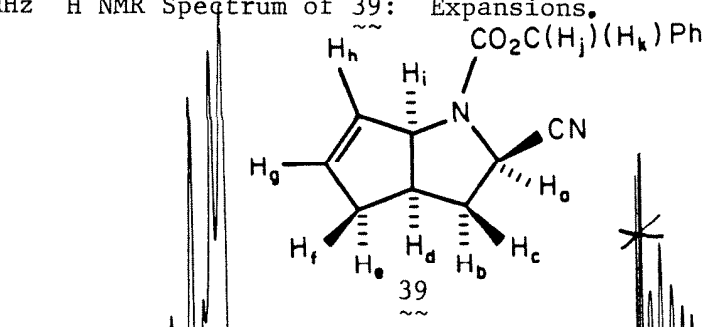


39

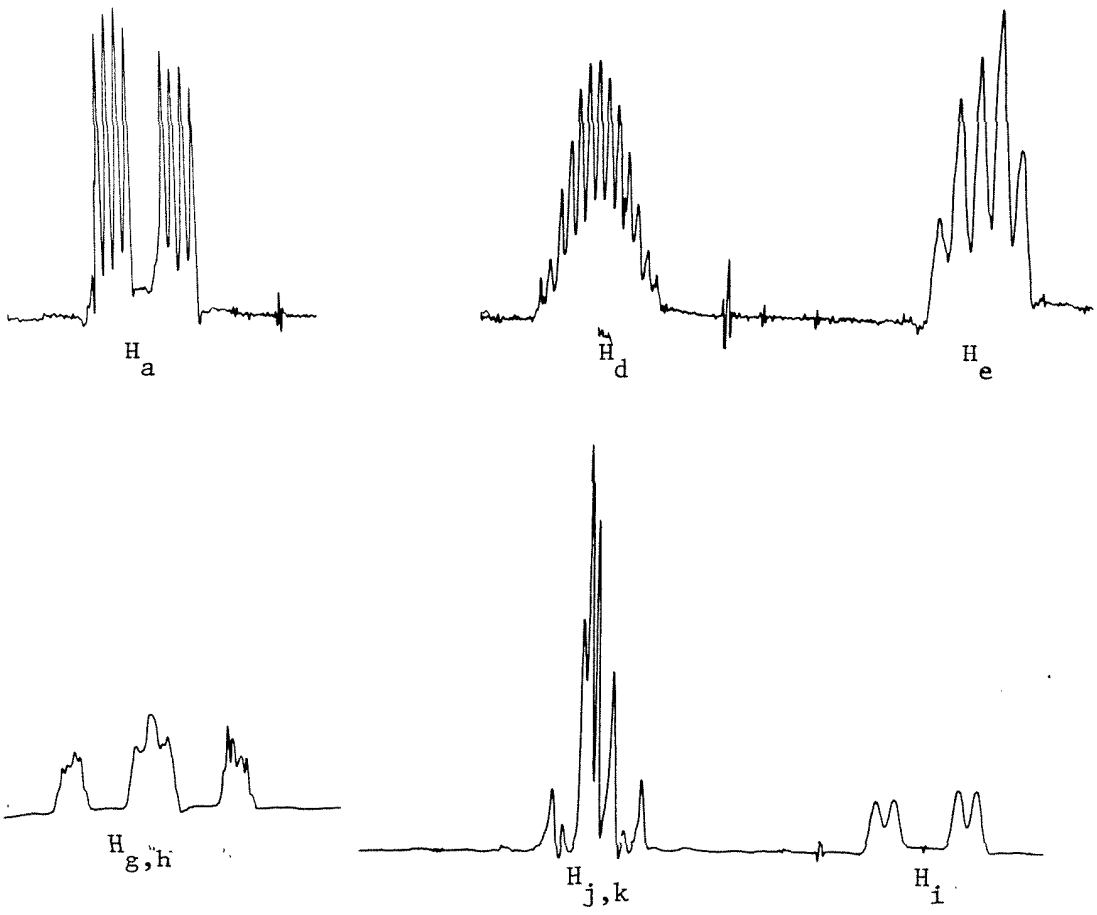
500 MHz ^{1}H NMR Spectrum of 39 ($CDCl_3$).

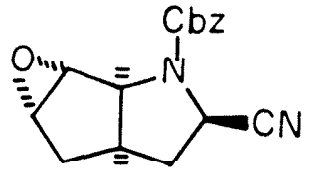


500 MHz ^{1}H NMR Spectrum of 39: Expansions.



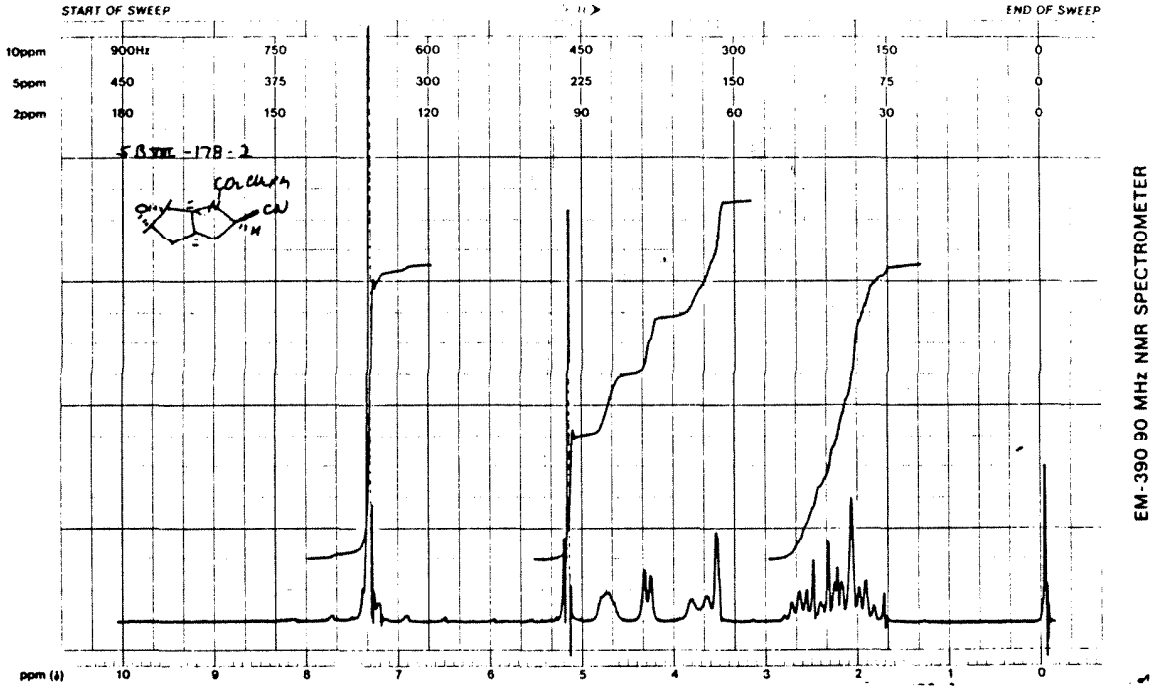
39



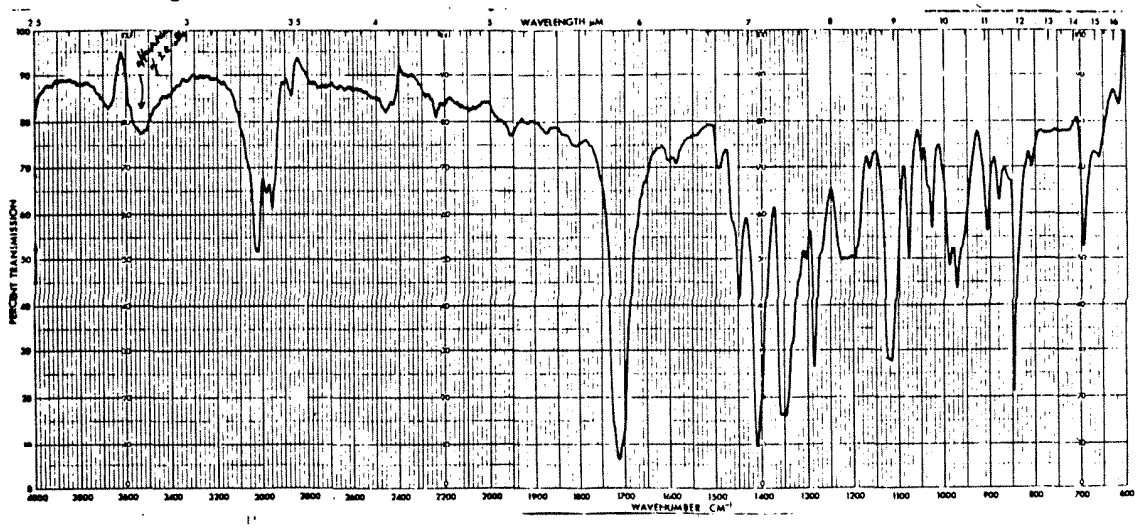


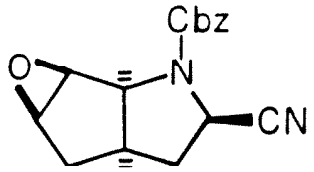
40

^{1}H NMR ($CDCl_3$)



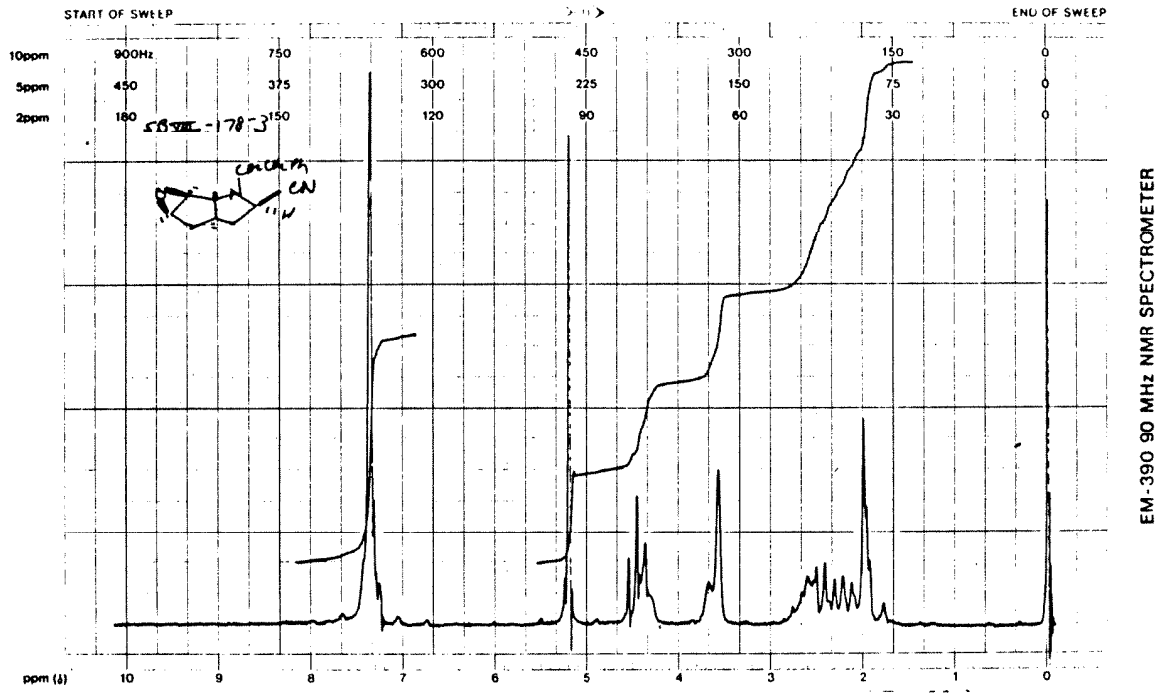
1R ($CHCl_3$)



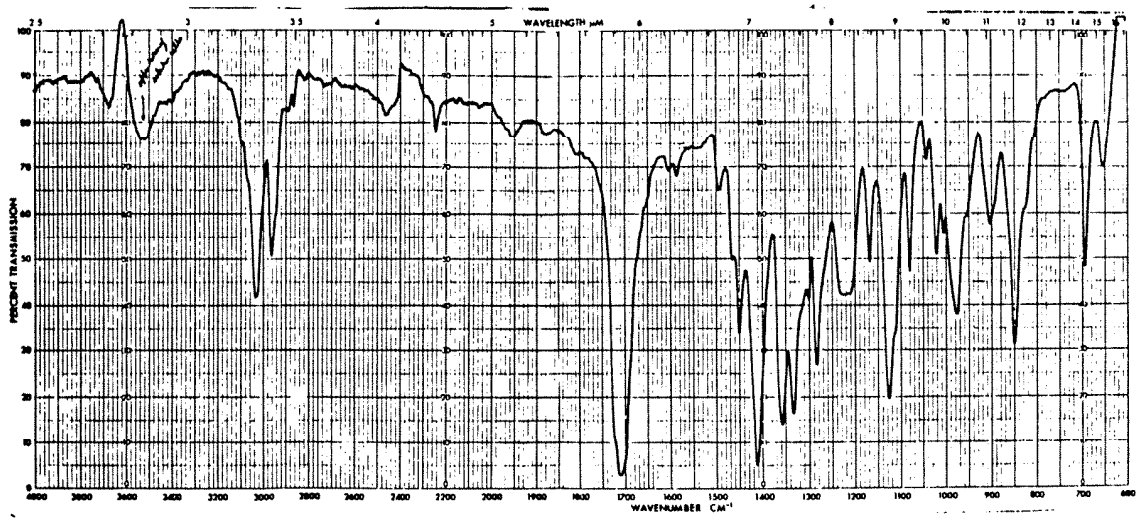


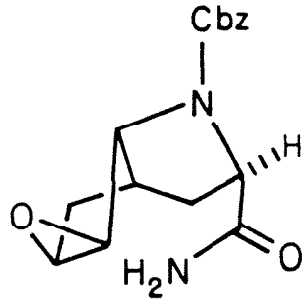
41

^{1}H NMR ($CDCl_3$)



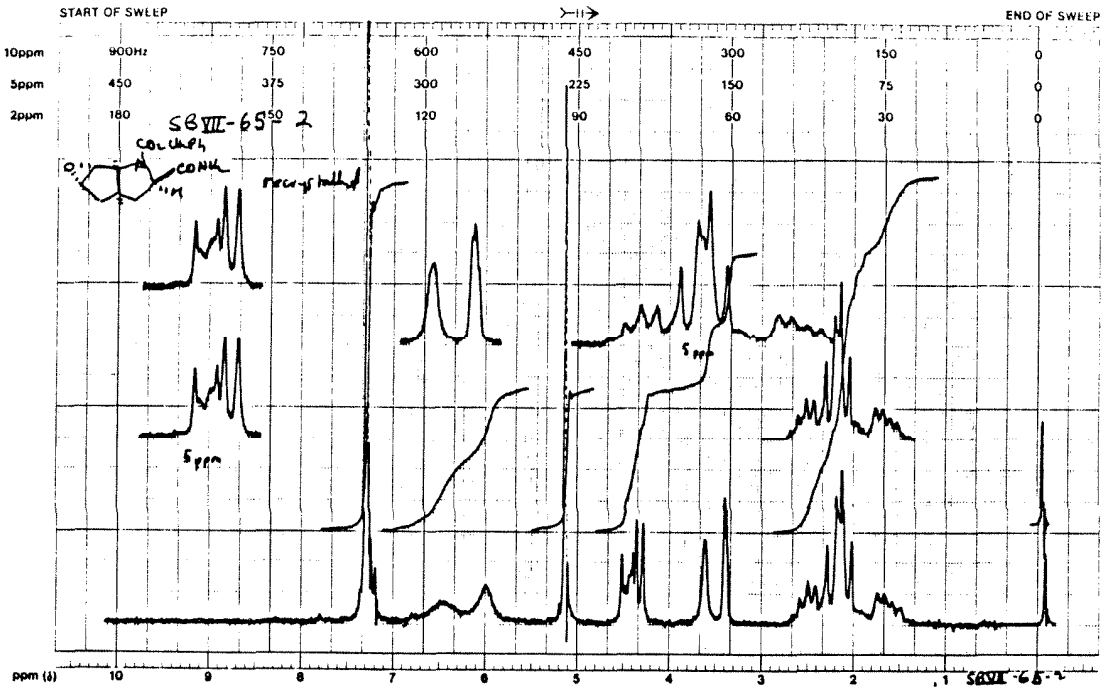
1R ($CHCl_3$)



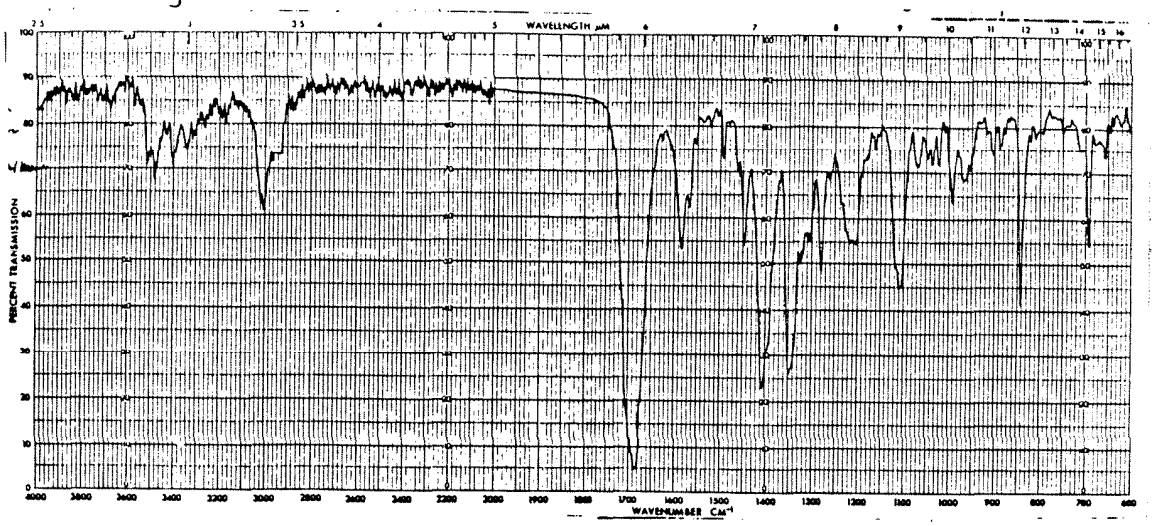


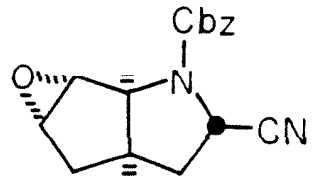
42

^{1}H NMR ($CDCl_3$)



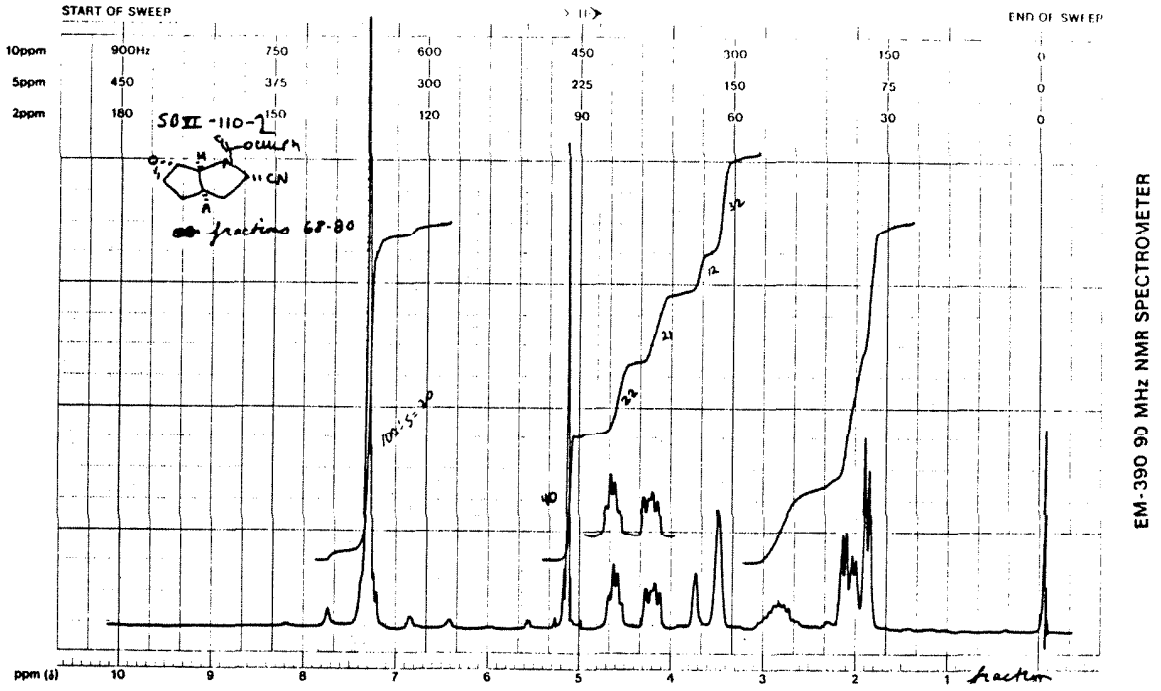
1R ($CHCl_3$)



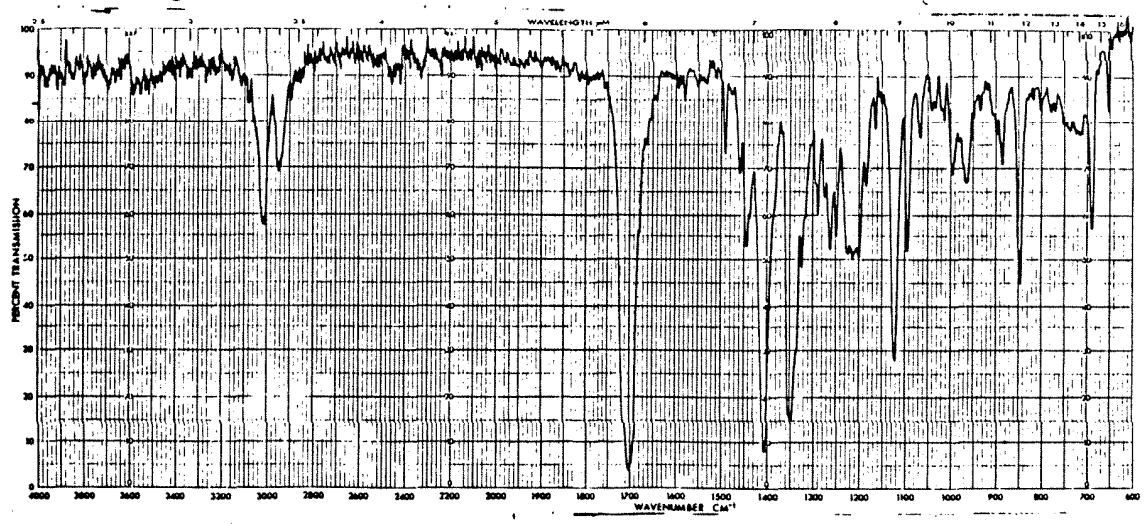


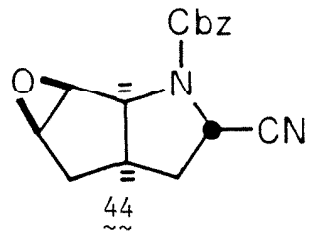
43

^{1}H NMR ($CDCl_3$)



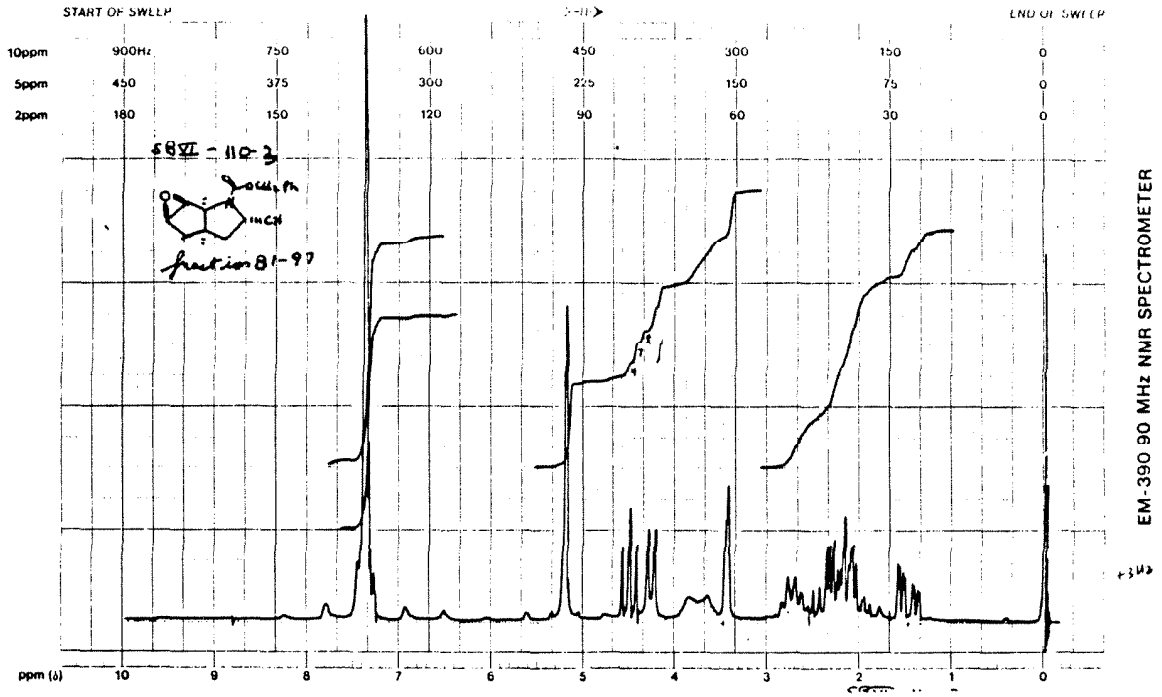
1R ($CHCl_3$)



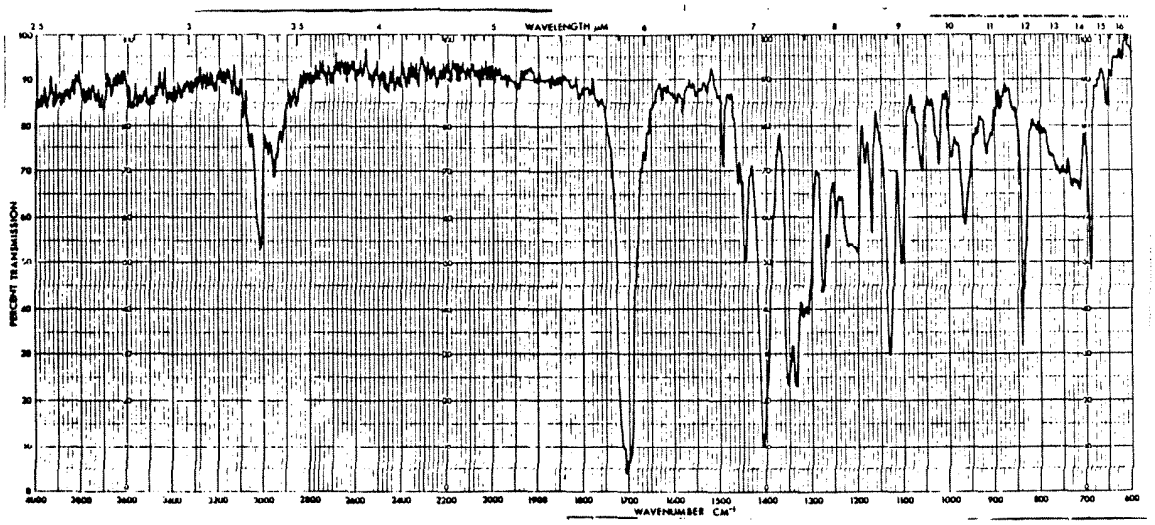


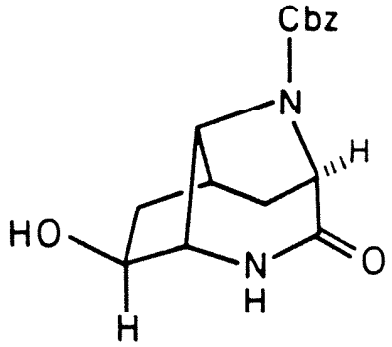
44

^{1}H NMR ($CDCl_3$)



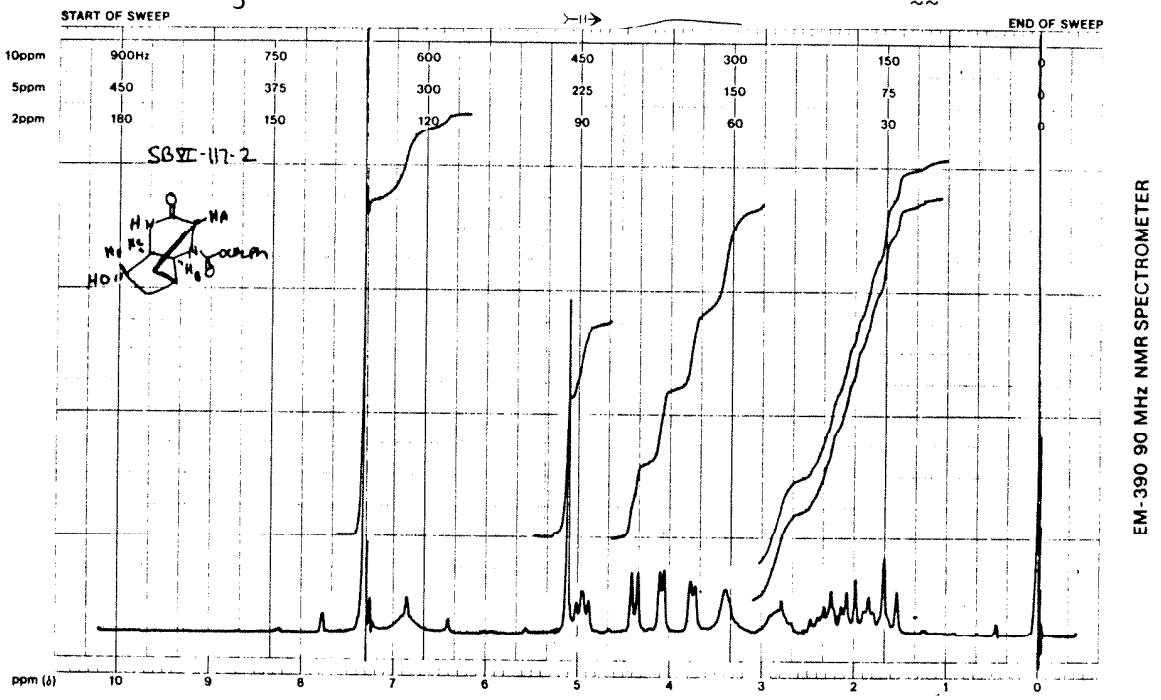
1R ($CHCl_3$)



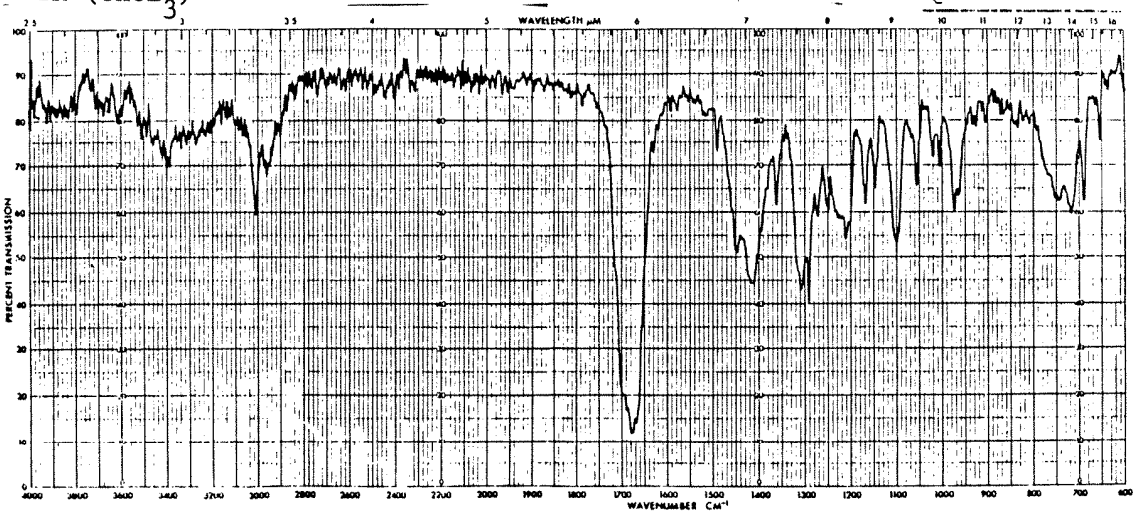


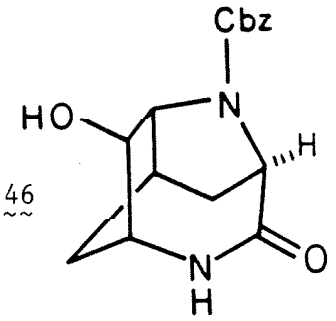
^{1}H NMR ($CDCl_3$)

45



1R ($CHCl_3$)

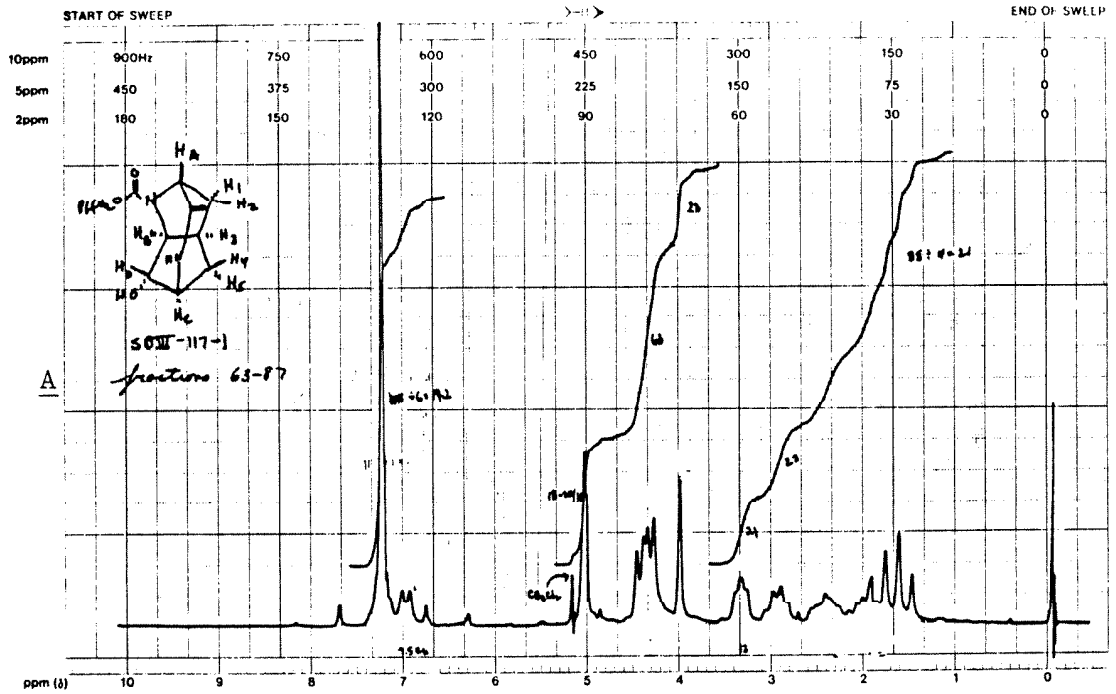


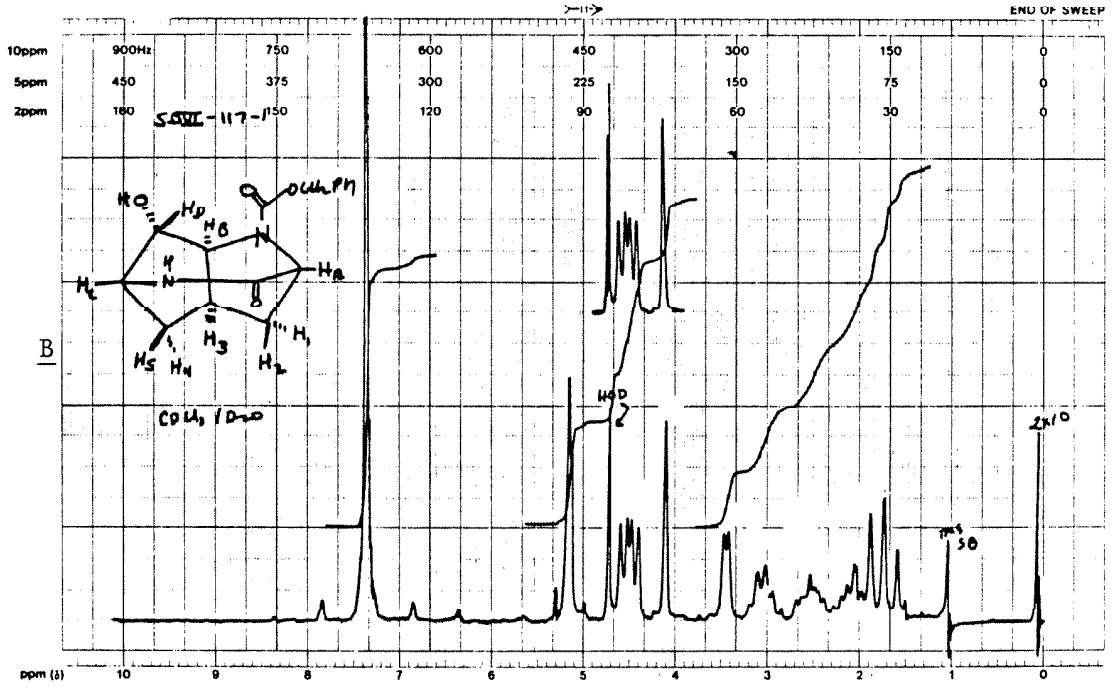


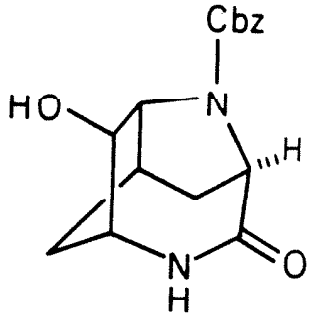
46

A. ^{1}H NMR ($CDCl_3$)

B. ^{1}H NMR ($CDCl_3$, D_2O)

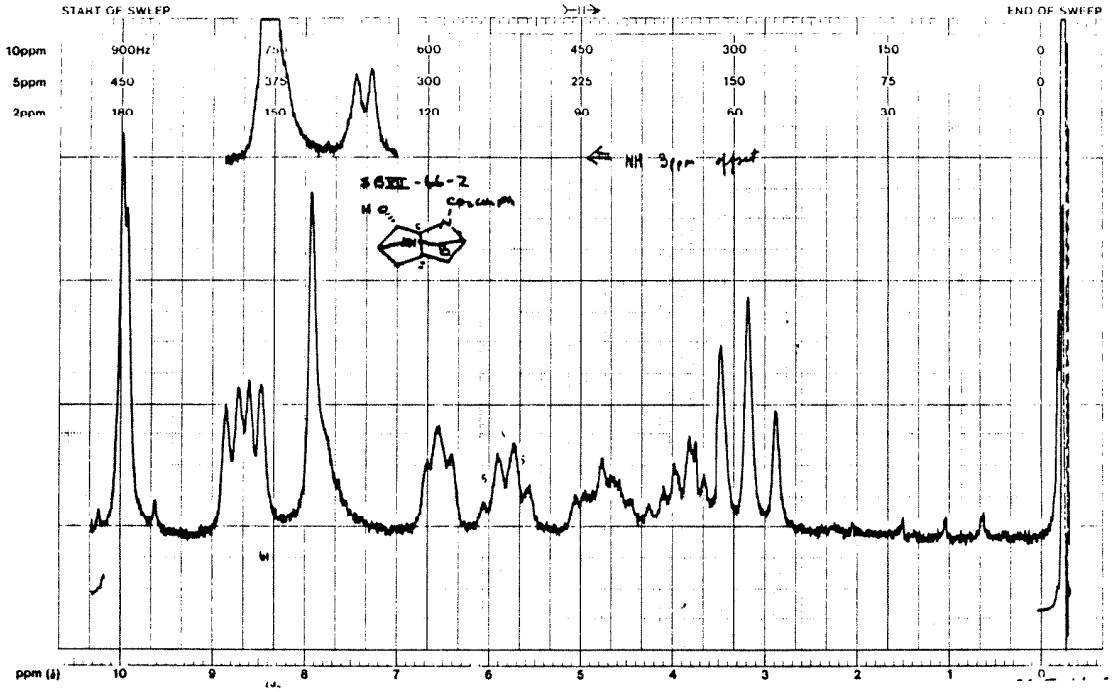






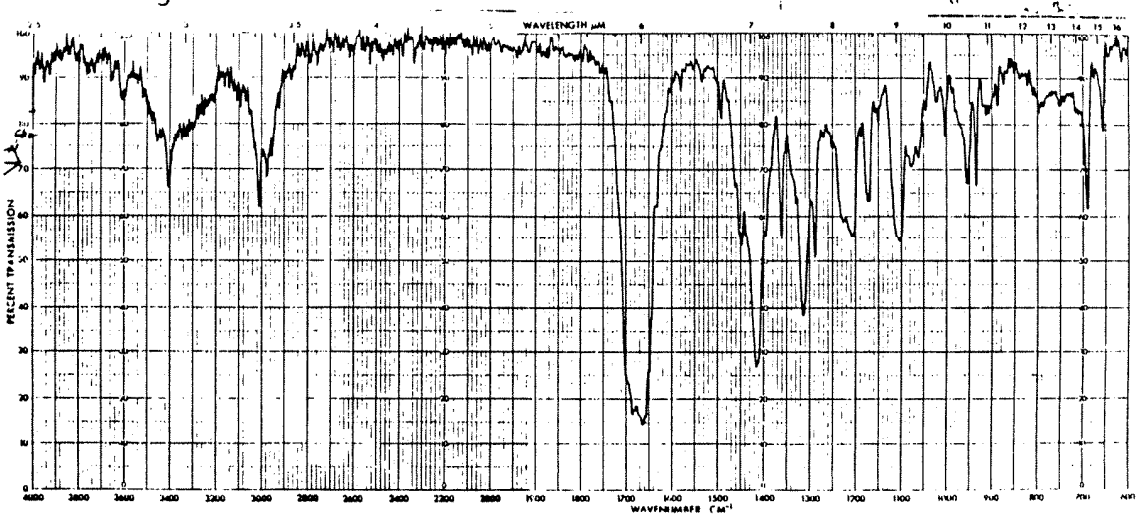
46

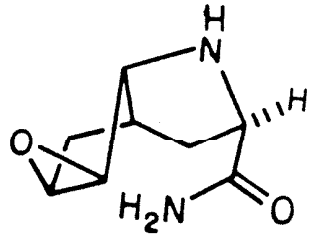
^{1}H NMR ($CDCl_3$) 5 ppm Sweep Width



EM-390 90 MHz NMR SPECTROMETER

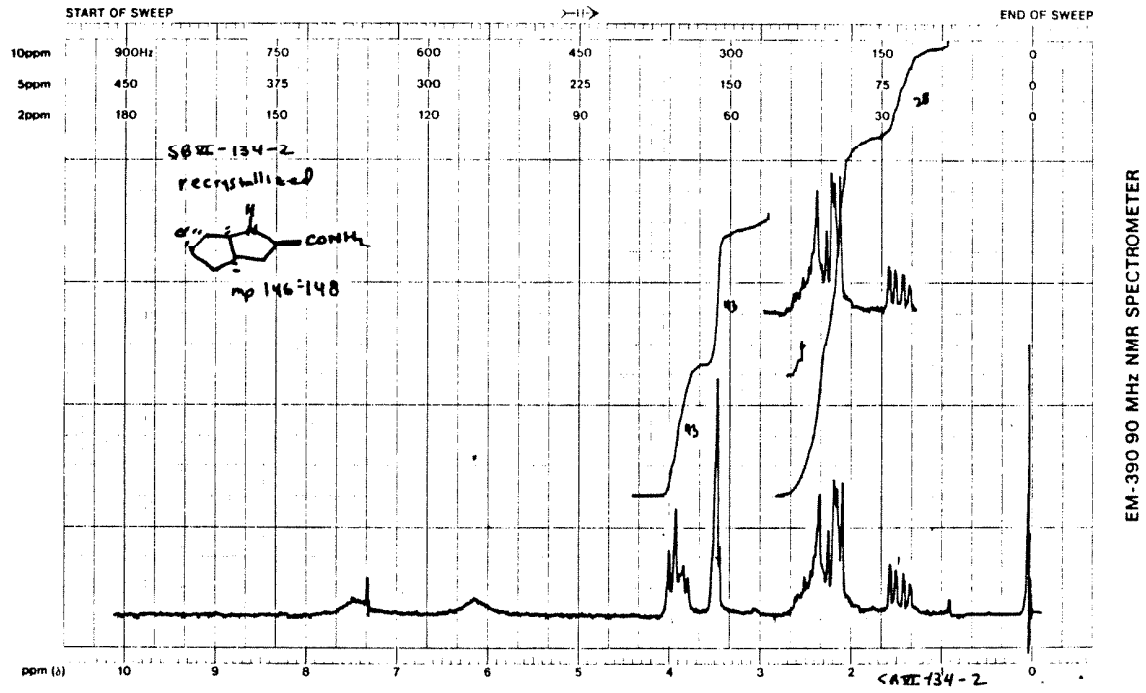
IR ($CHCl_3$)



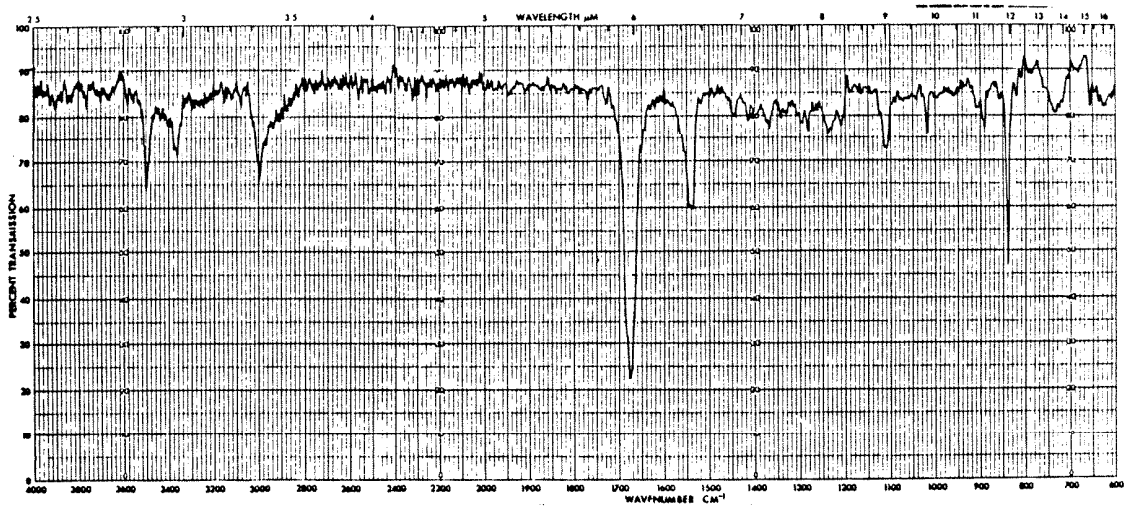


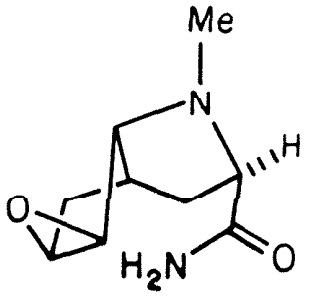
47a

^{1}H NMR ($CDCl_3$)



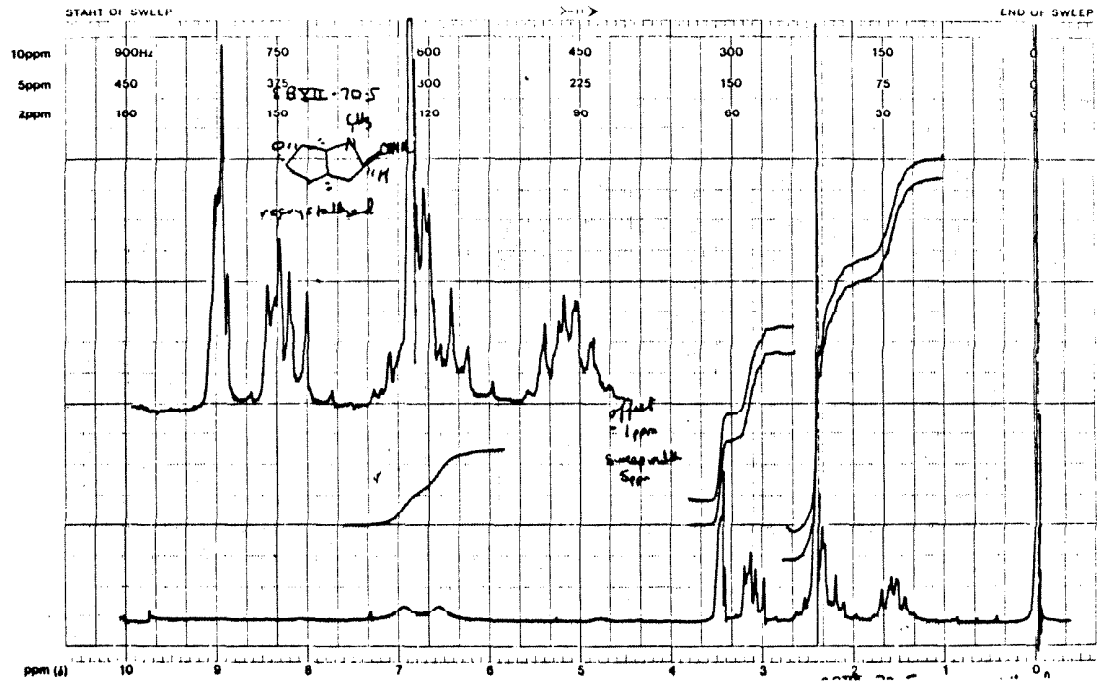
1R ($CHCl_3$)



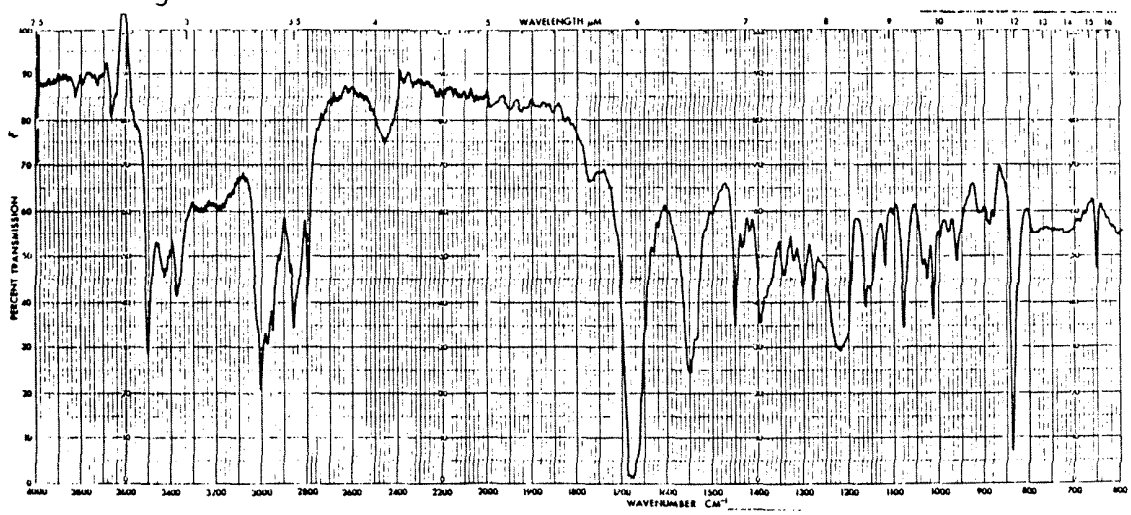


47b

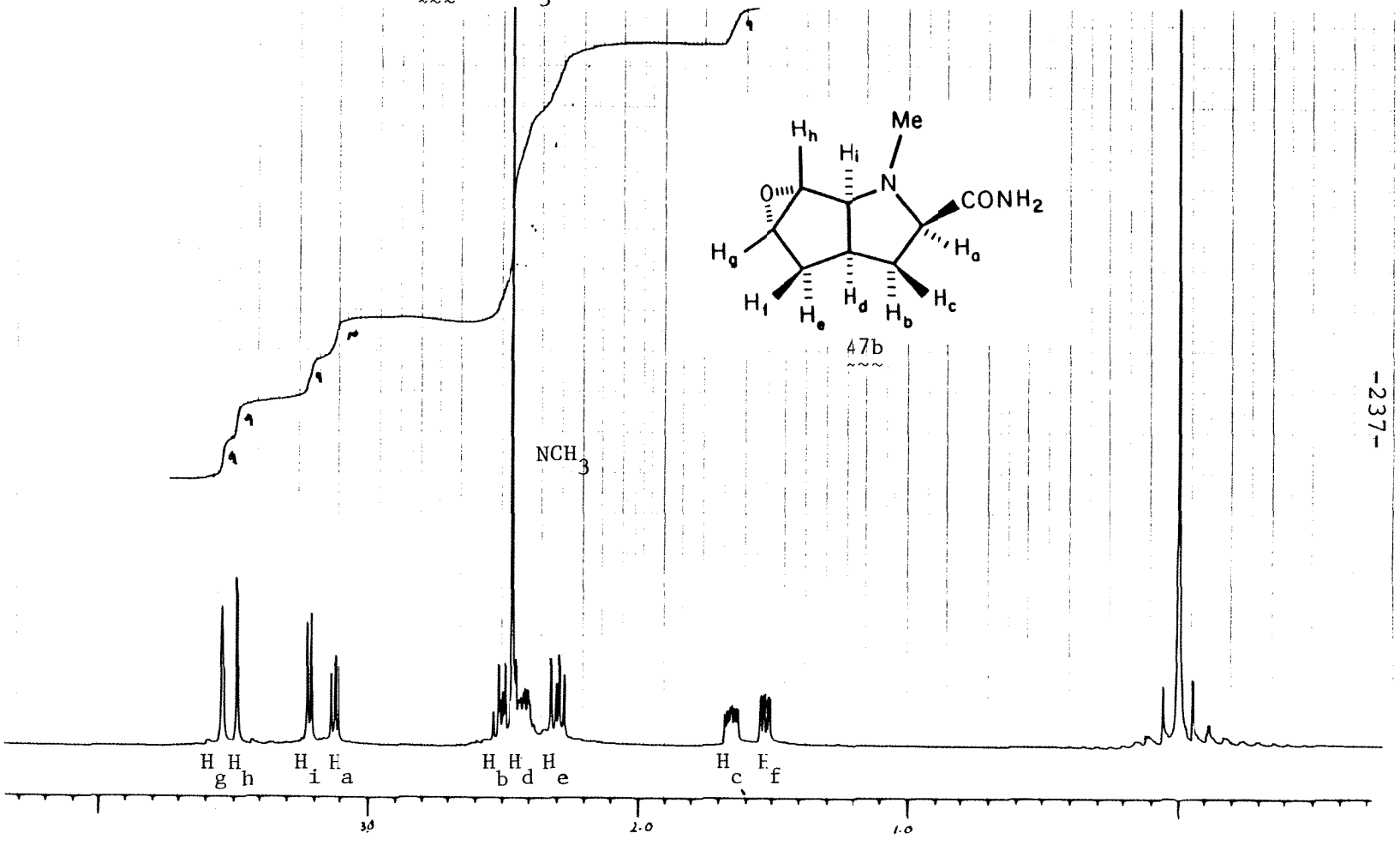
^1H NMR ($CDCl_3$)



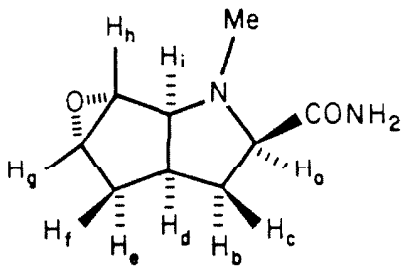
IR ($CHCl_3$)



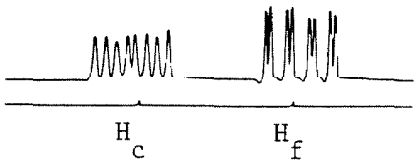
500 MHz ^{1}H NMR Spectrum of 47b ($CDCl_3$).

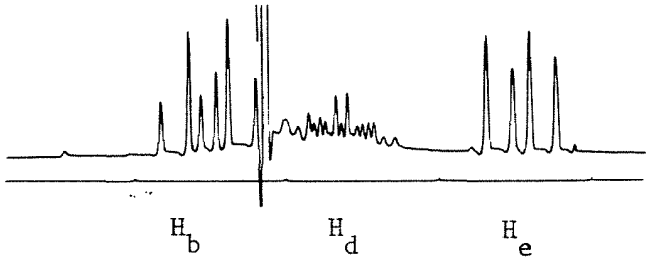


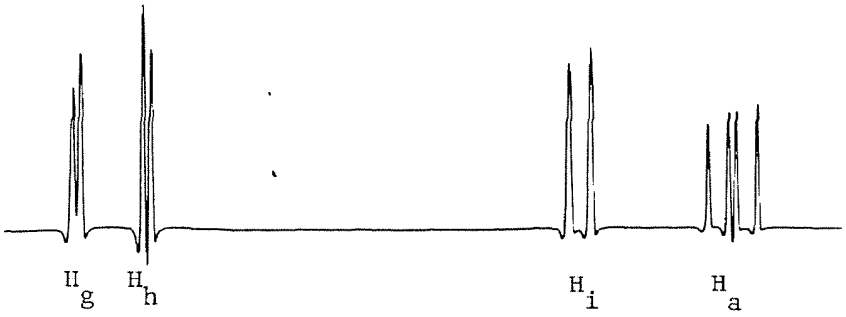
500 MHz ^{1}H NMR Spectrum of 47b: Expansions.

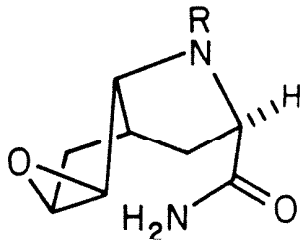


47b





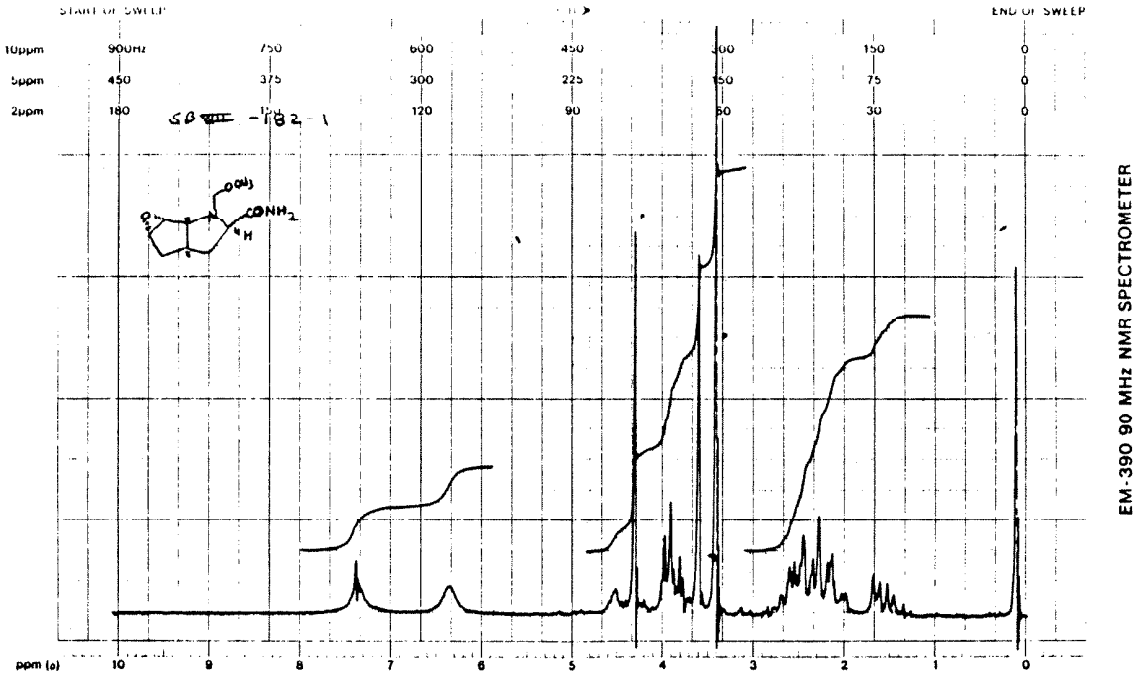


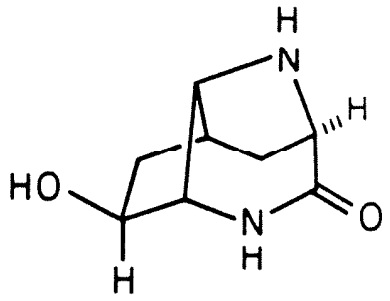


47c

R = CH_2OMe

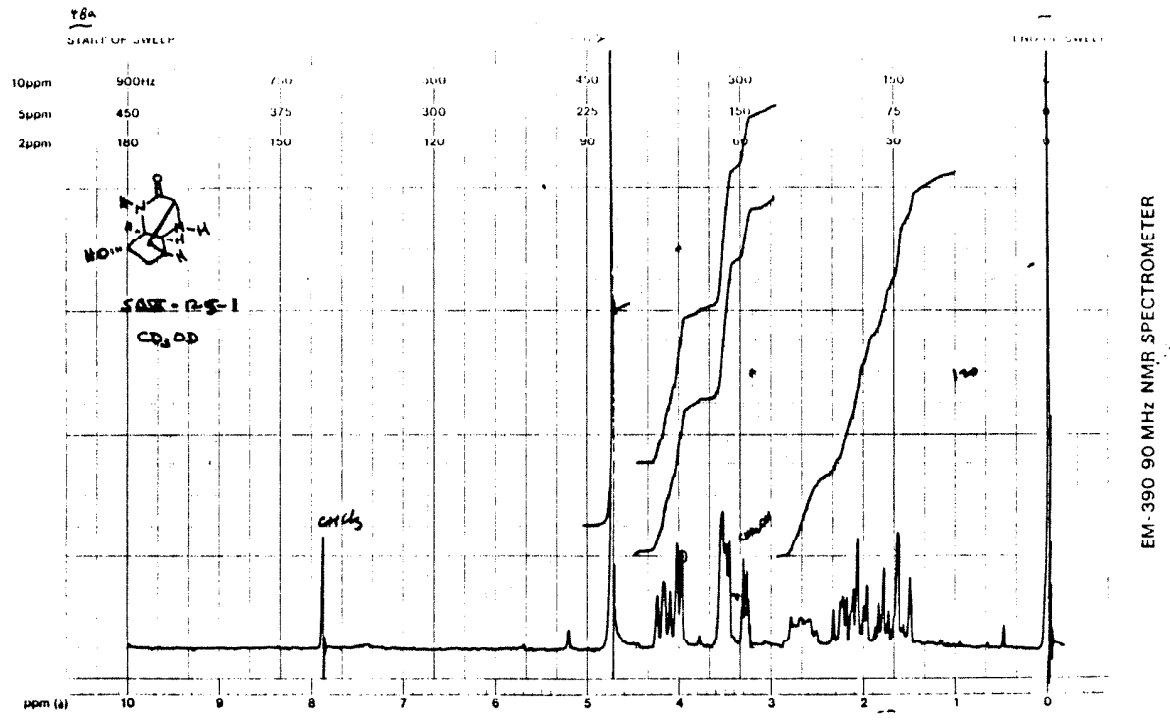
^1H NMR ($CDCl_3$)

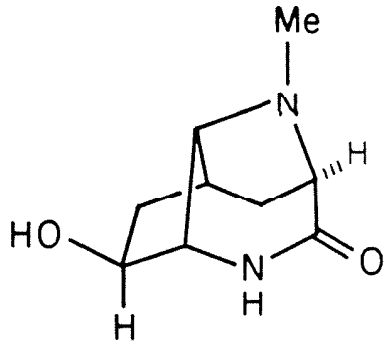




48a

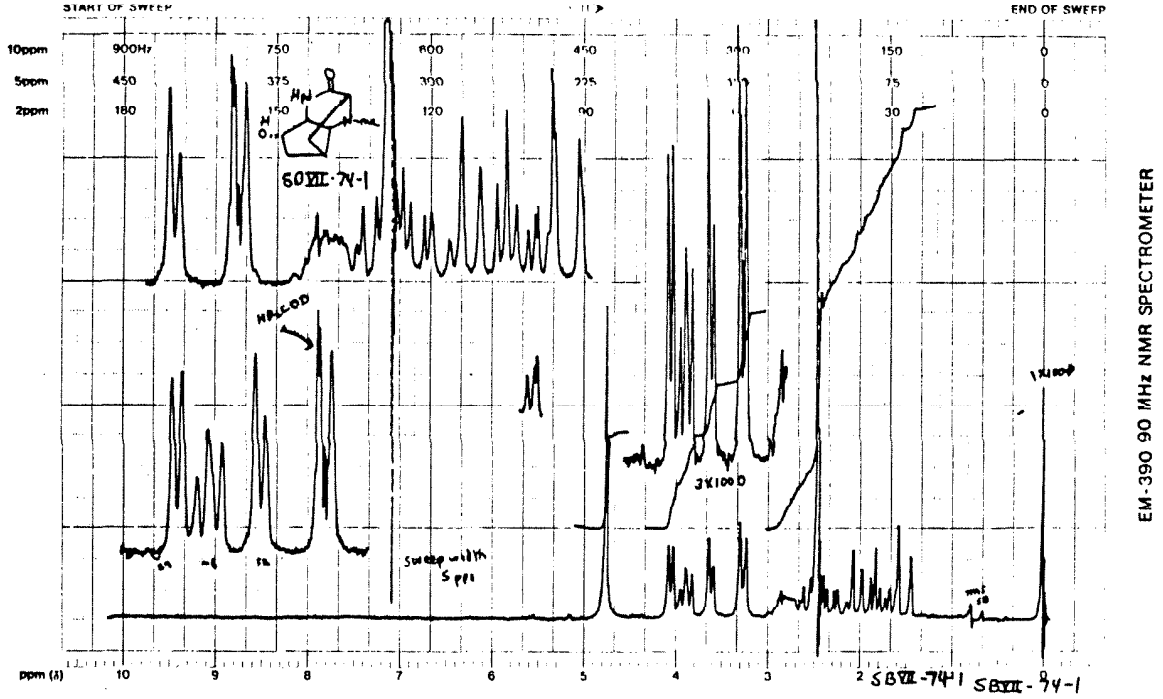
^{1}H NMR (CD_3OD)



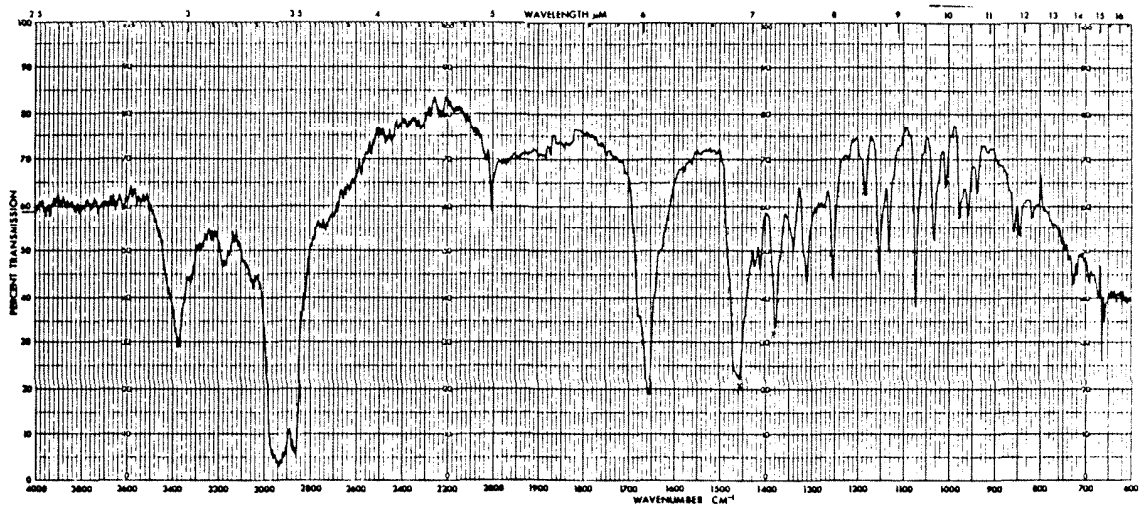


48b

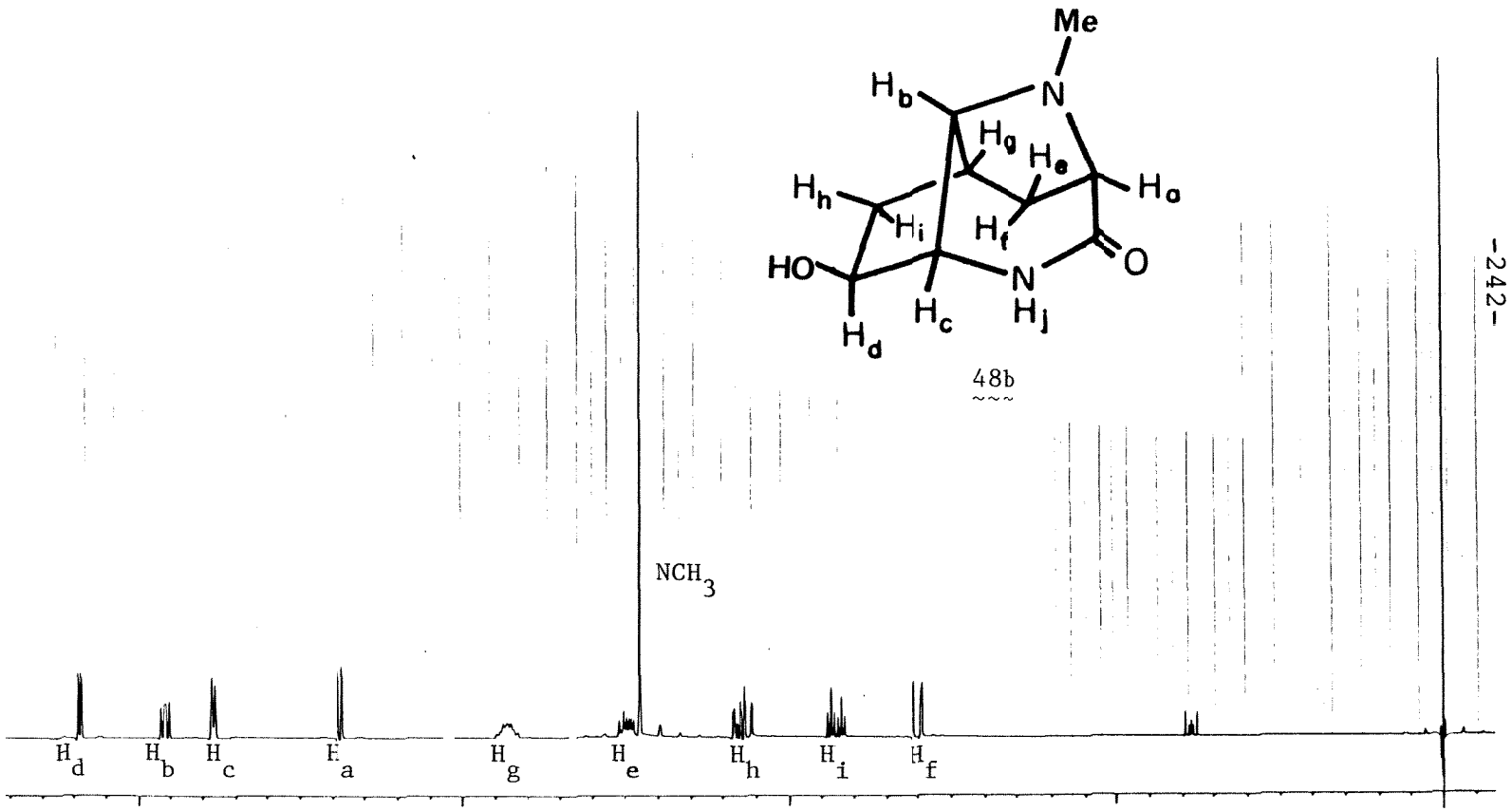
^{1}H NMR (CD_3OD)



1R (Nujol)

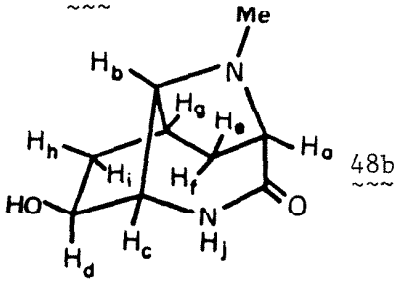


500 MHz ^{1}H NMR Spectrum of 48b (D_2O).

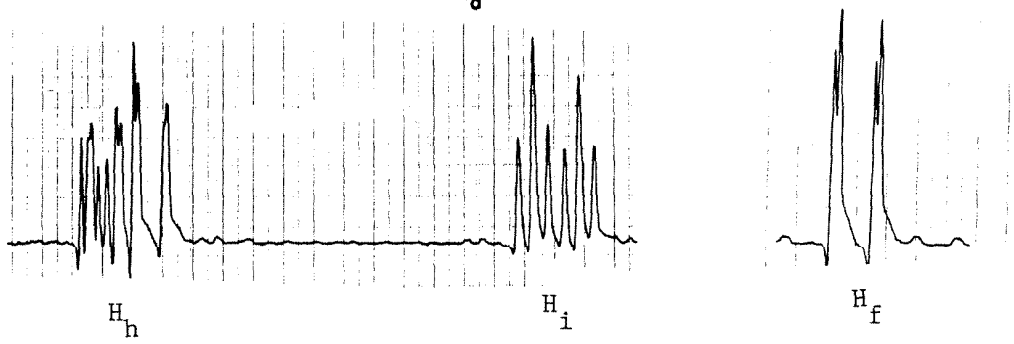


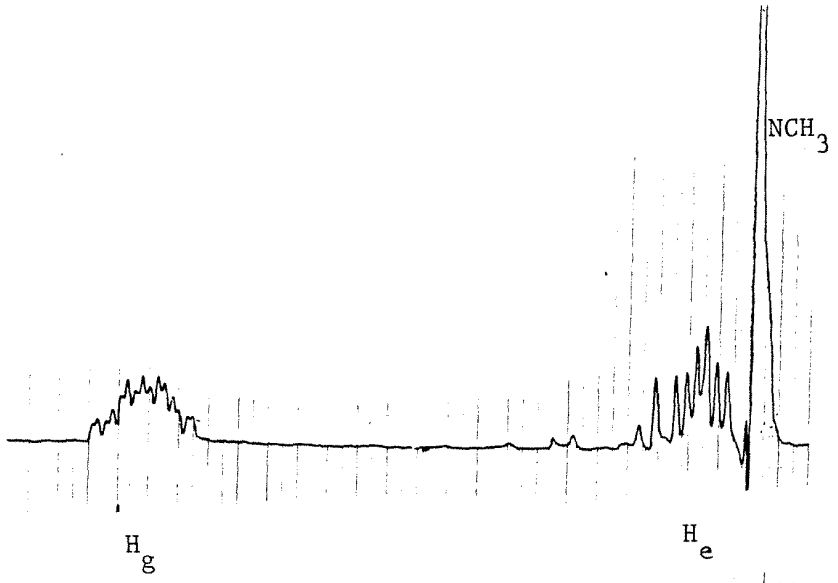
48b

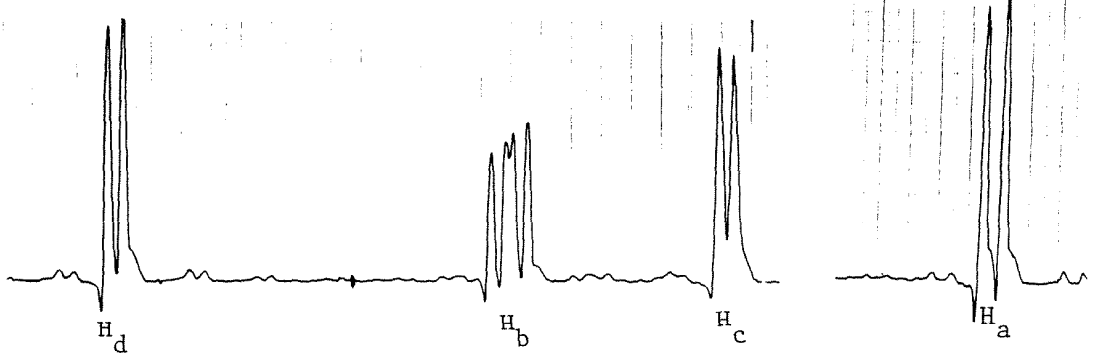
500 MHz ^{1}H NMR Spectra of 48b: Expansions.

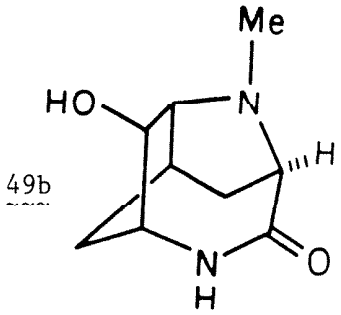


48b



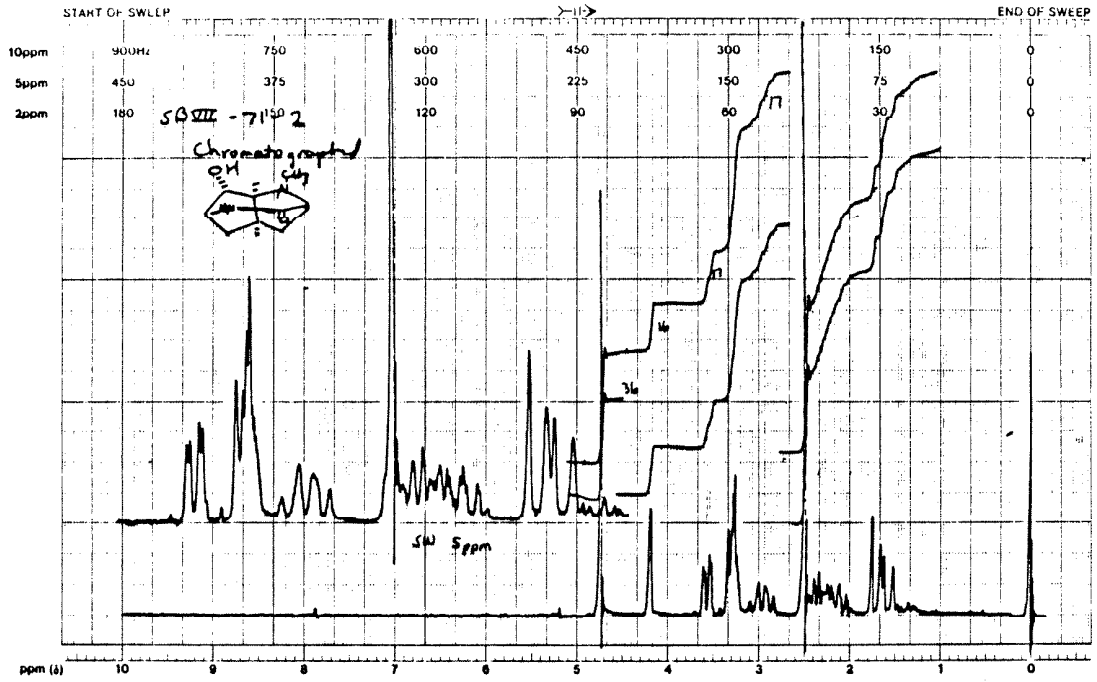




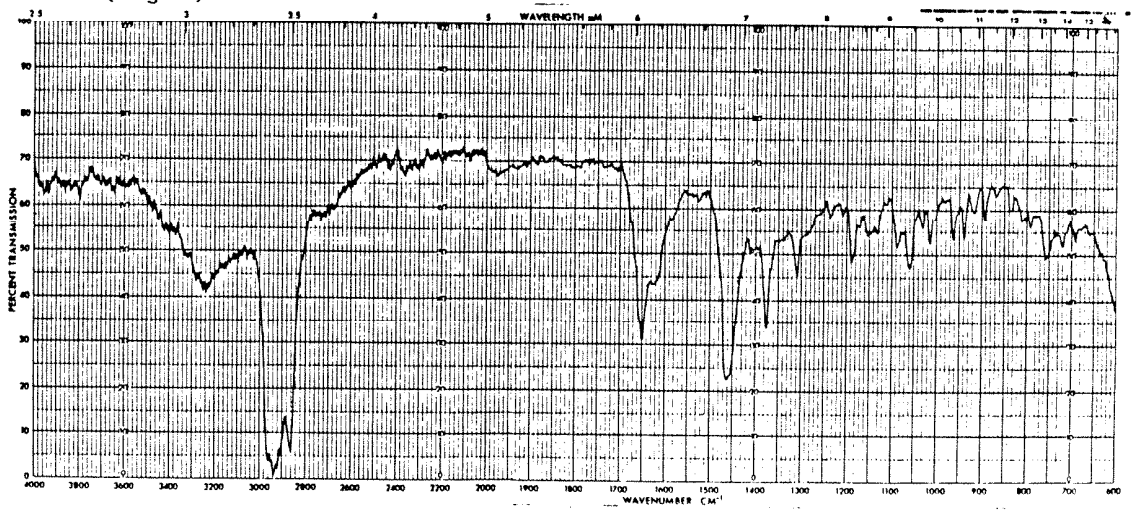


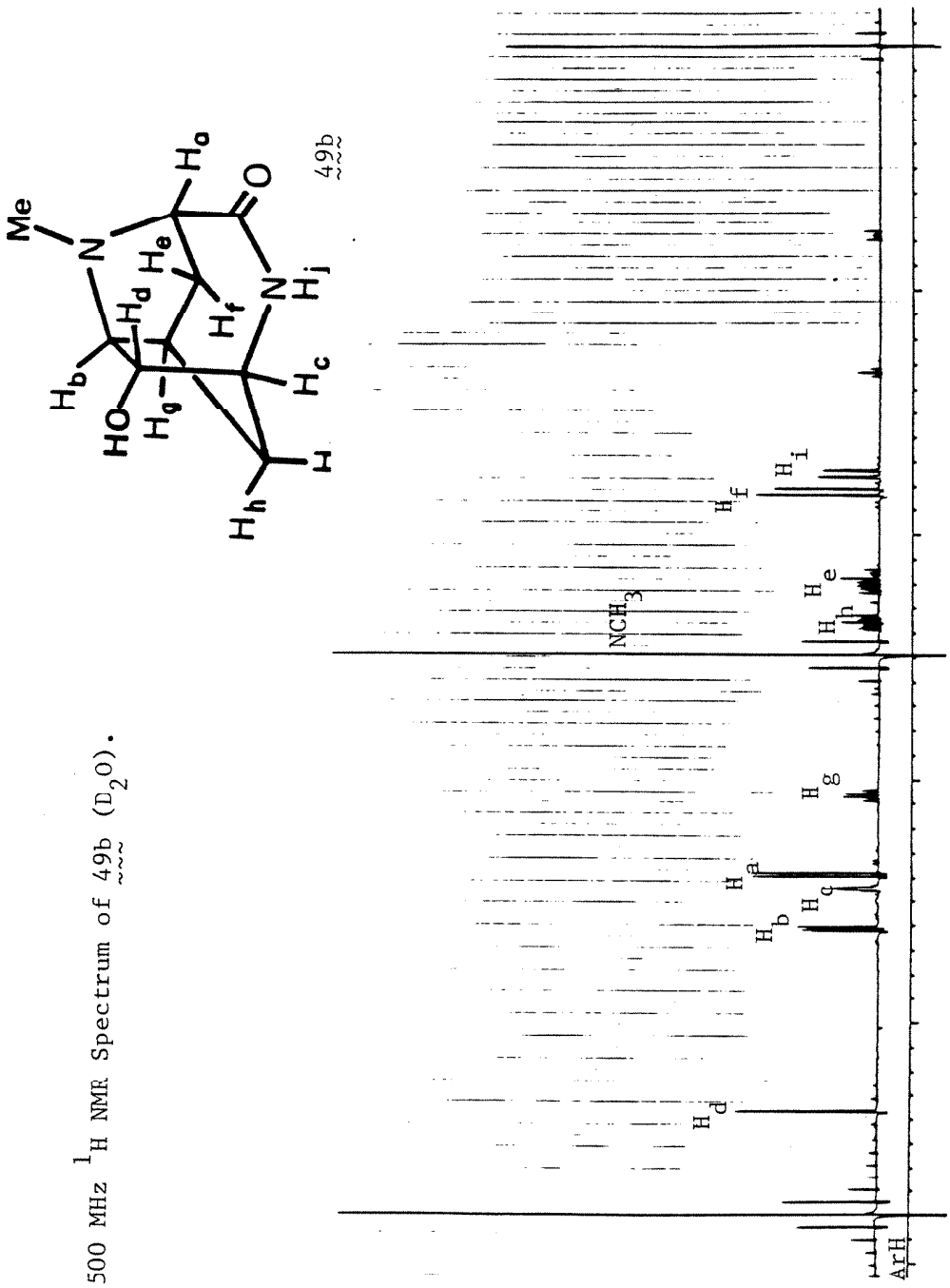
49b

^{1}H NMR (CD_3OD)



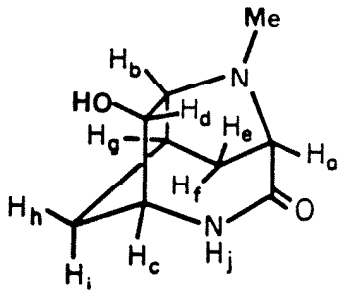
IR (Nujol)



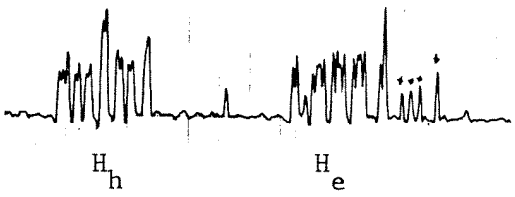


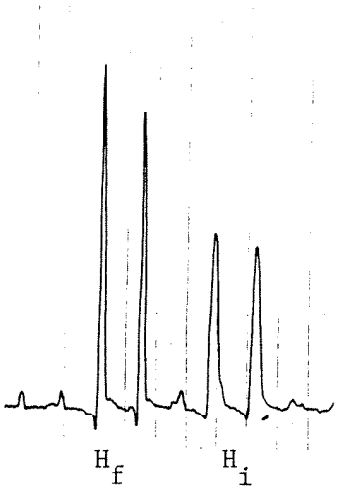
500 MHz ^{1}H NMR Spectrum of 49b (D_2O).

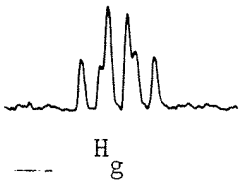
500 MHz ^{1}H NMR Spectrum of 49b: Expansions.

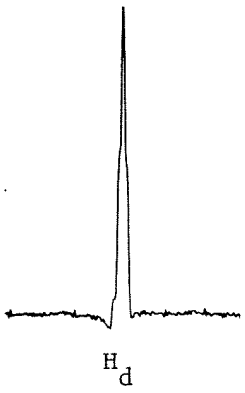


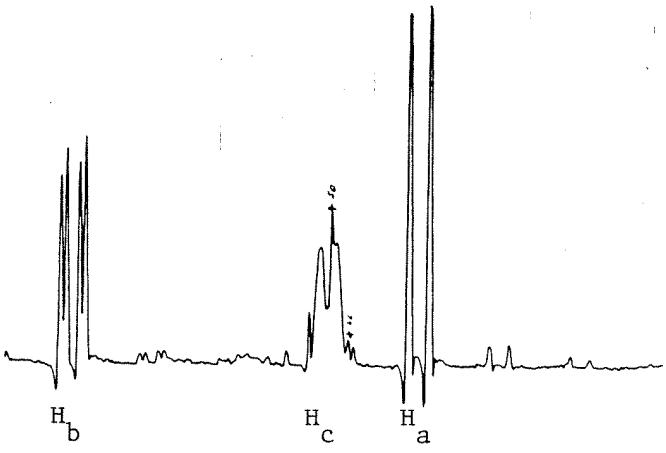
49b

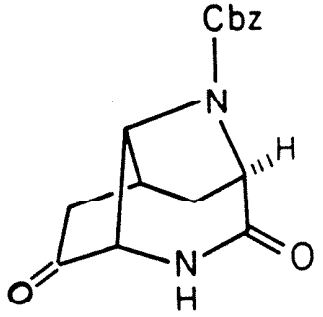






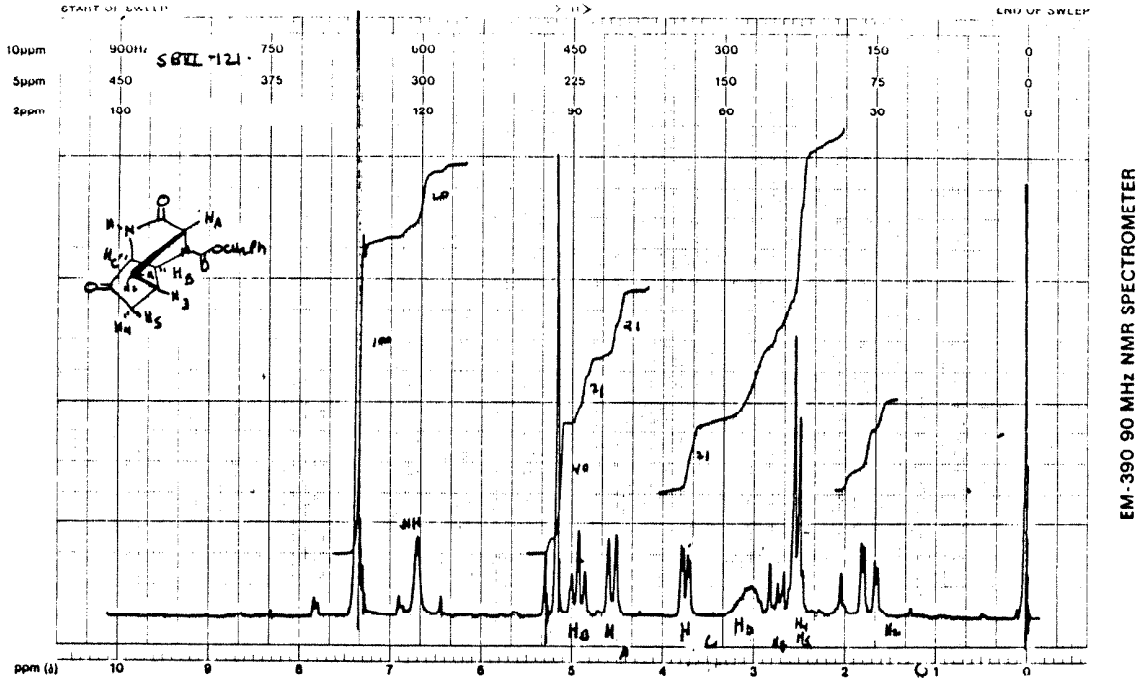




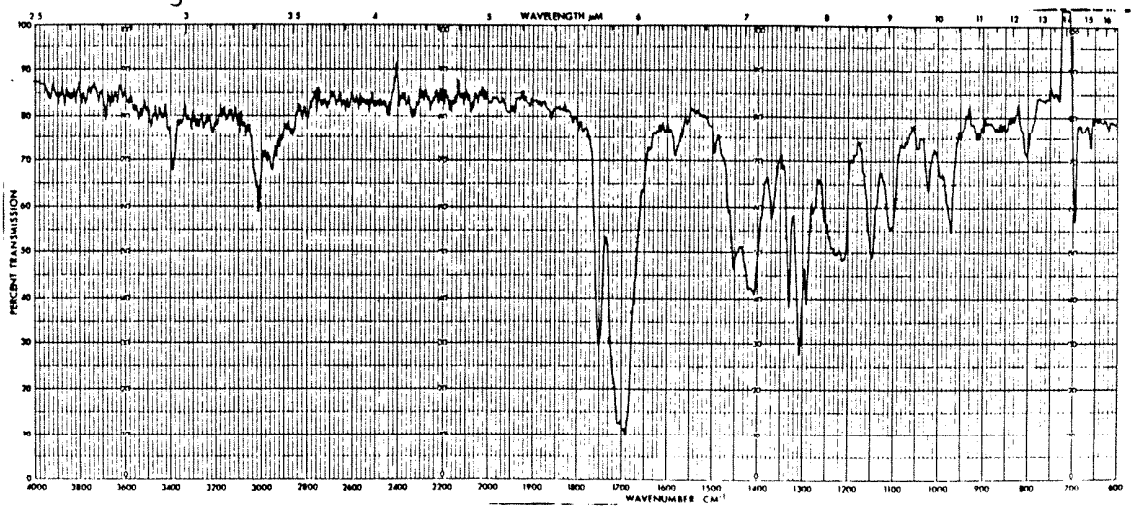


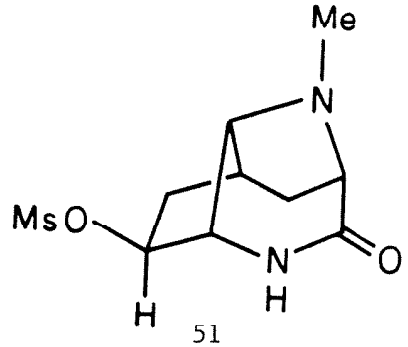
^{1}H NMR ($CDCl_3$)

50



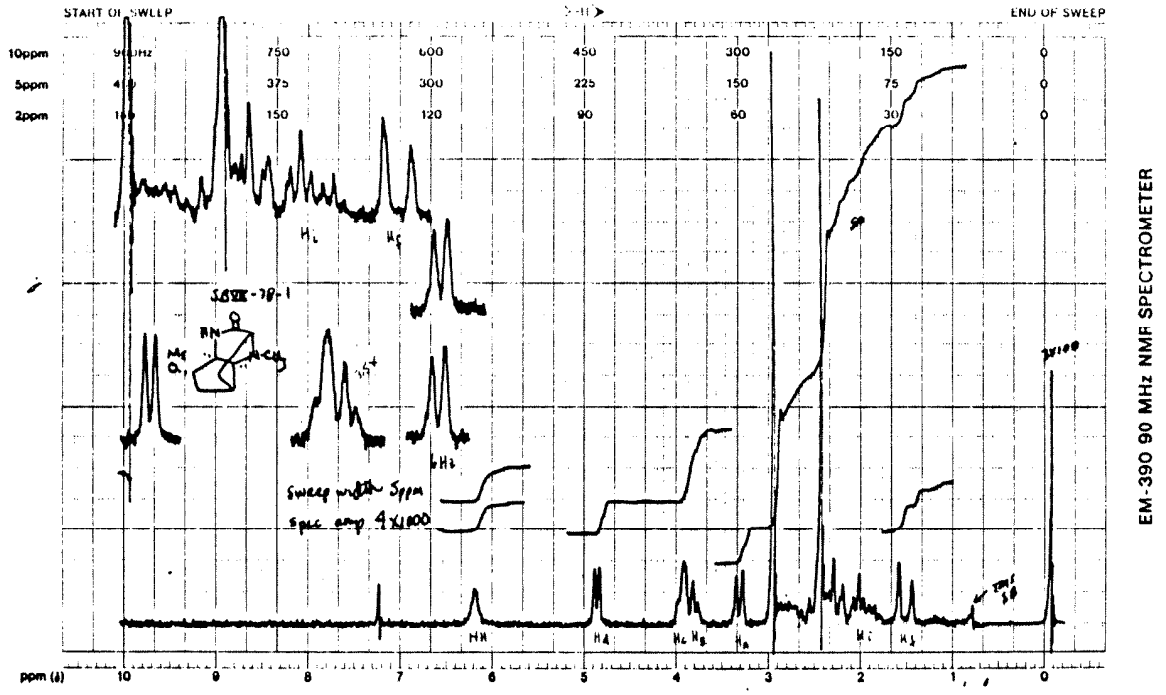
1R ($CHCl_3$)



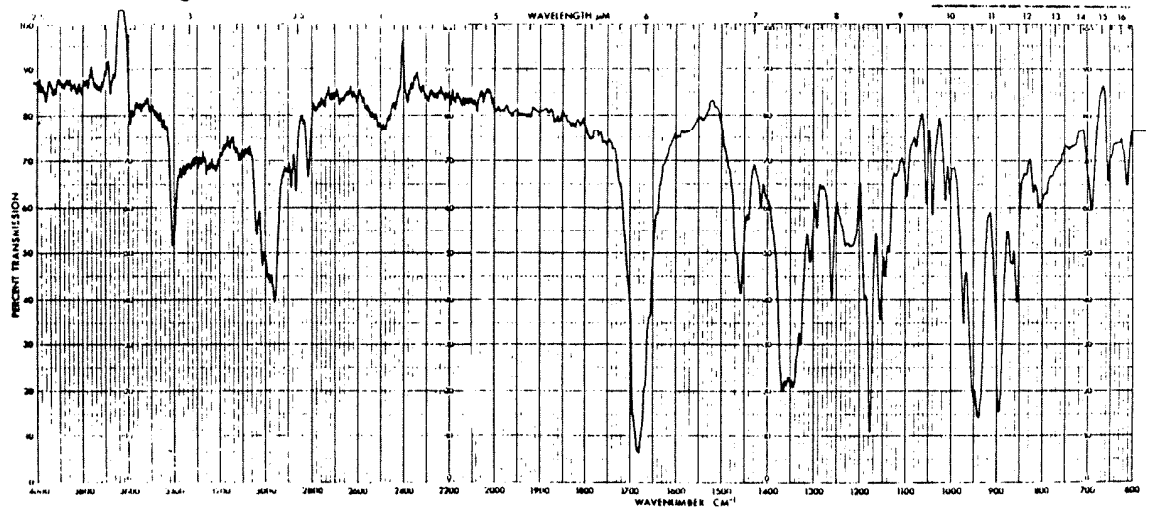


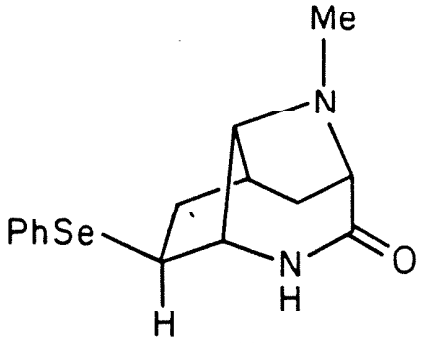
51

^{1}H NMR ($CDCl_3$)



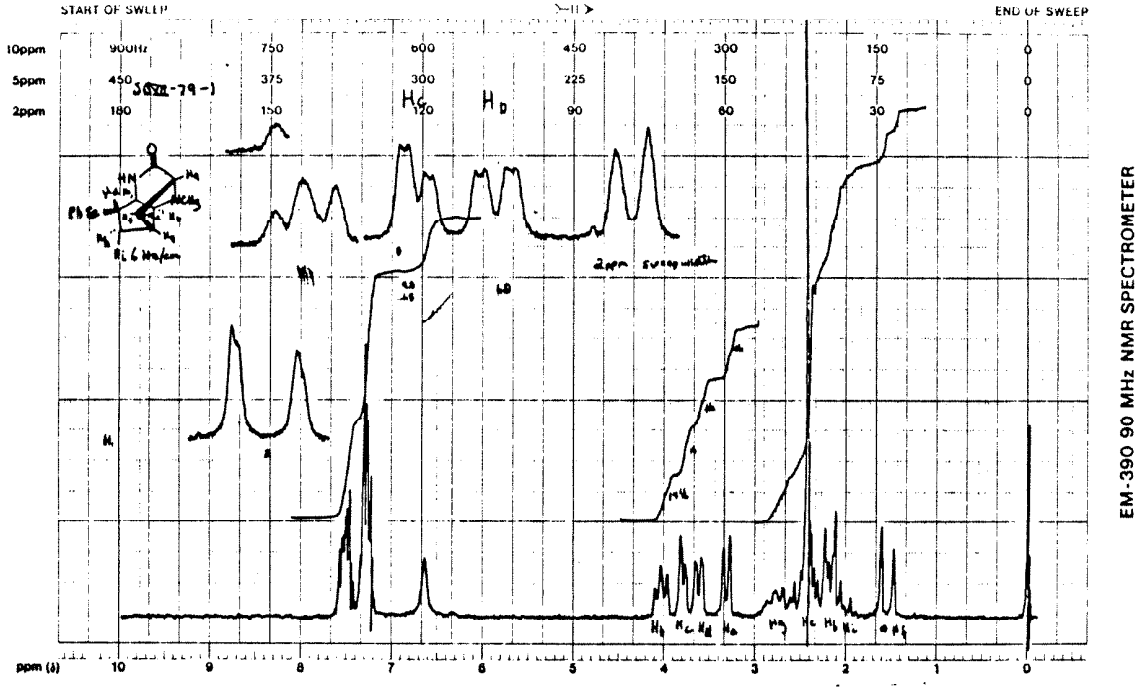
IR ($CHCl_3$)



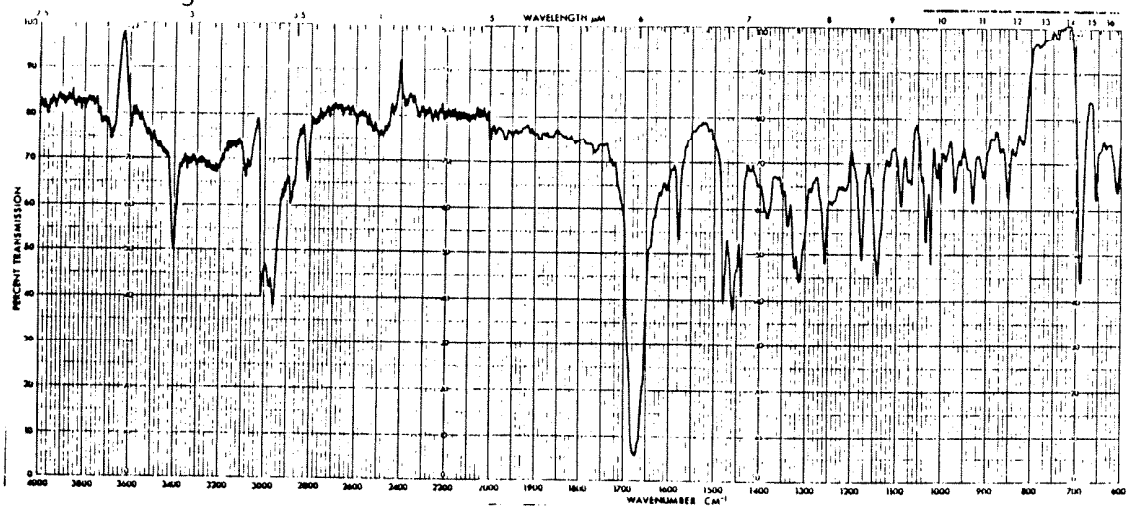


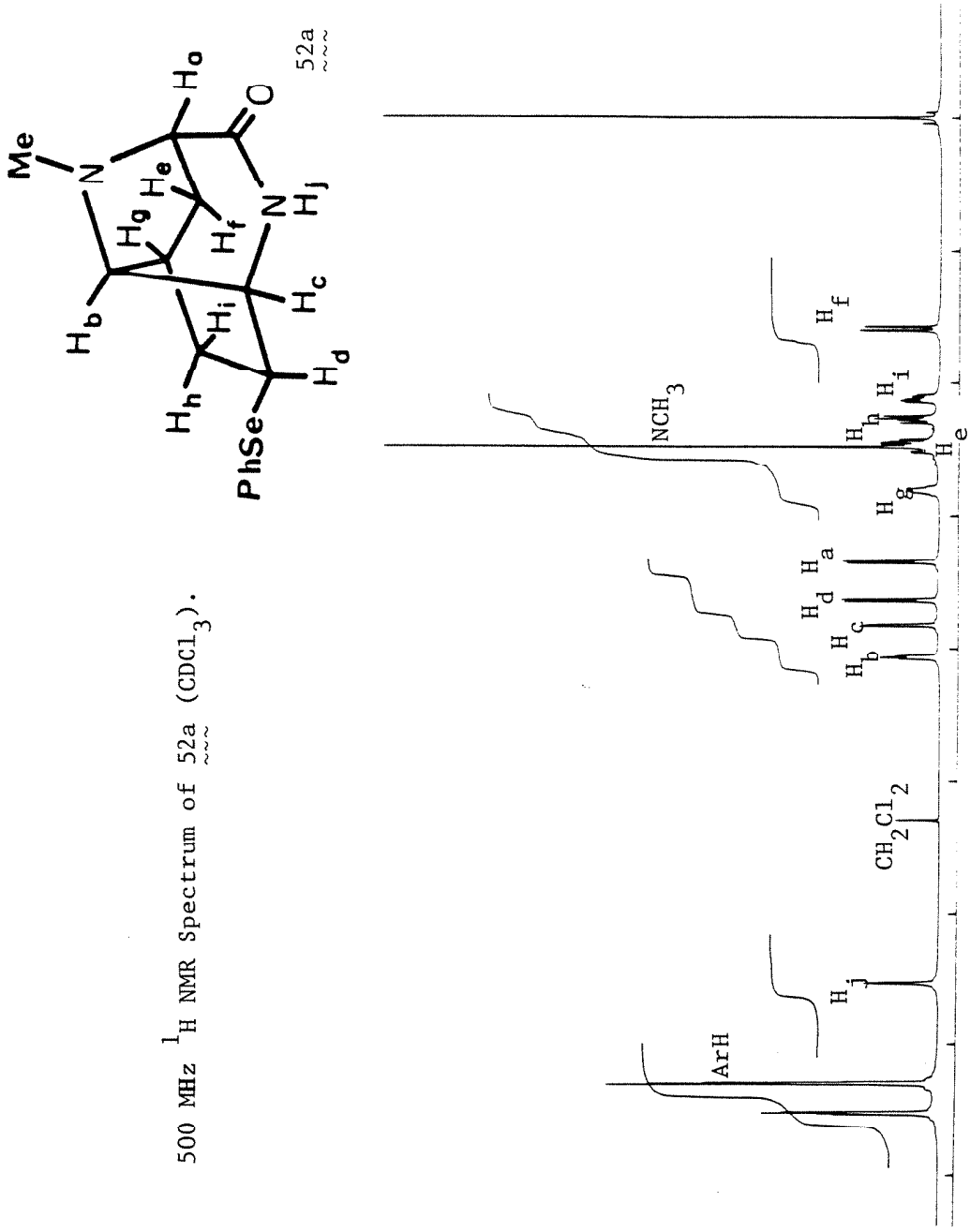
52a

^{1}H NMR ($CDCl_3$)



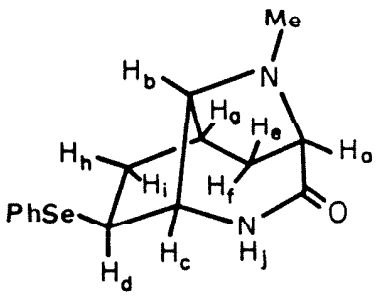
IR ($CHCl_3$)



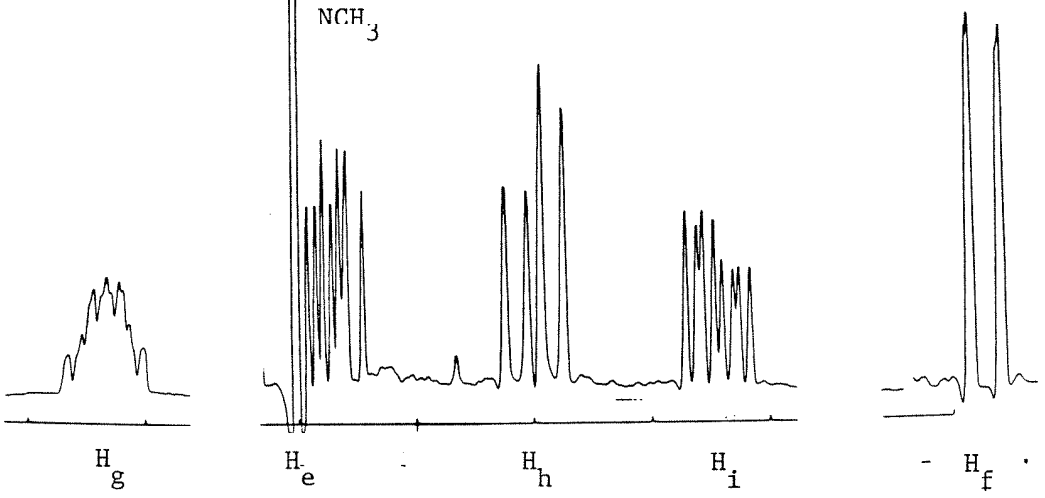


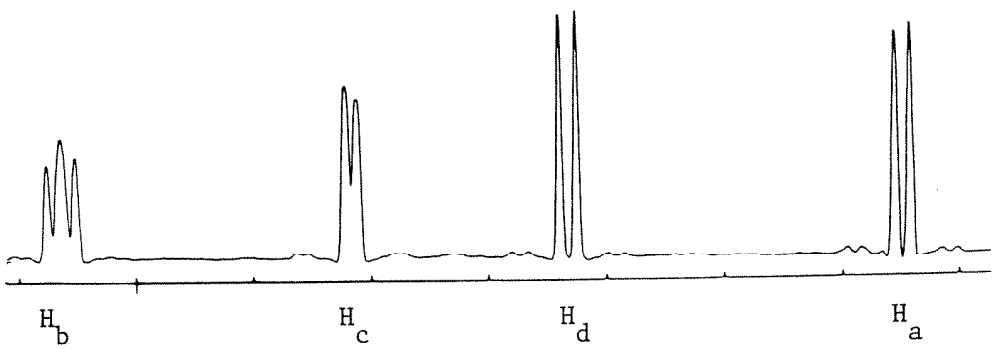
500 MHz ^1H NMR Spectrum of 52a ($CDCl_3$).

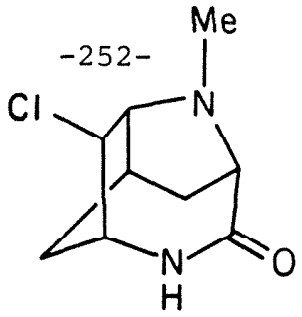
500 MHz ^{1}H NMR Spectrum of 52a: Expansions.



52a

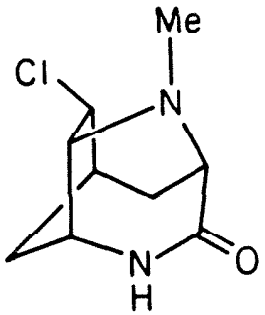






54b

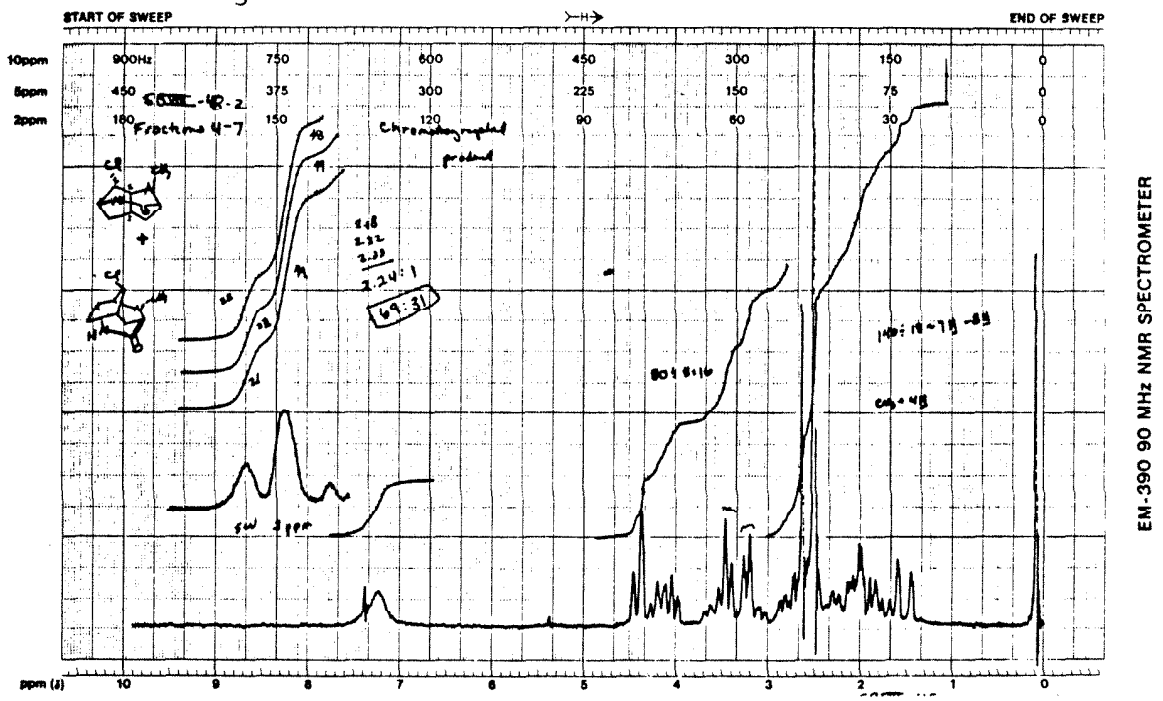
and



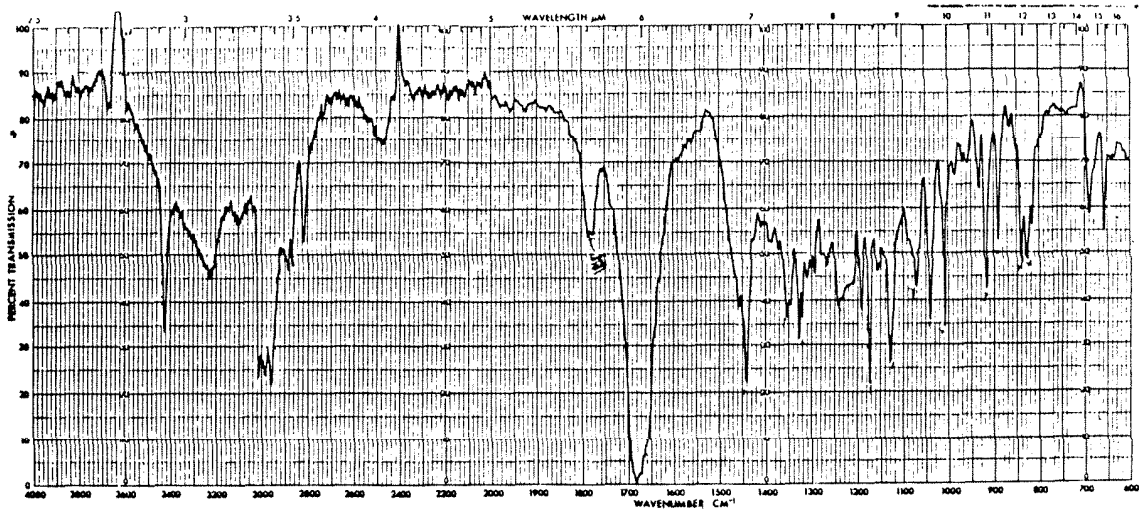
55

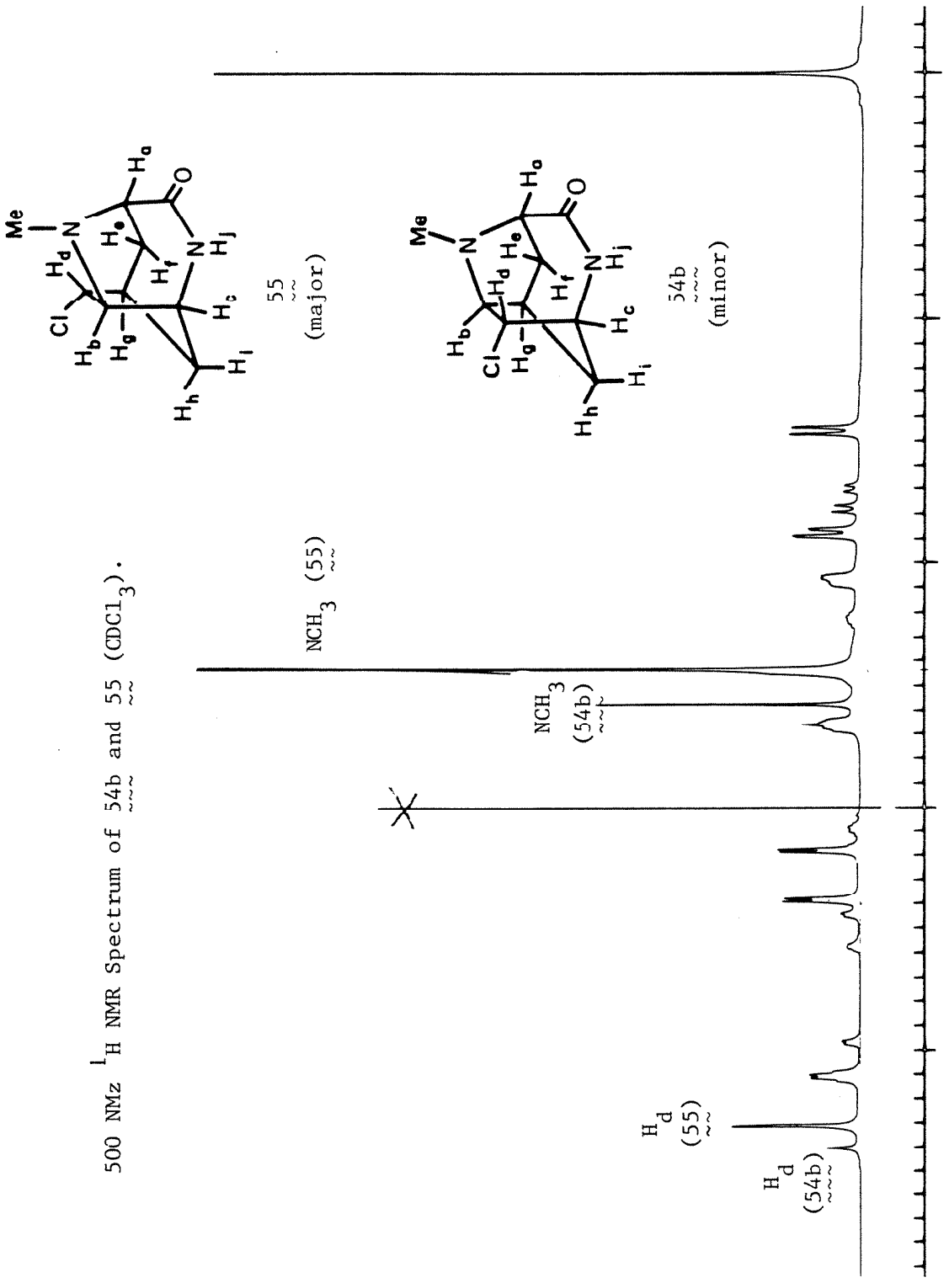
^{1}H NMR ($CDCl_3$)

54b:55 = 31:69



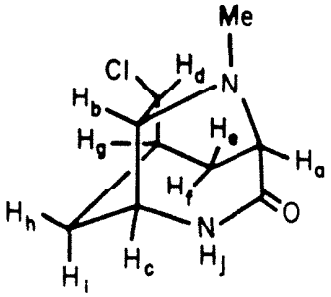
1R ($CHCl_3$)



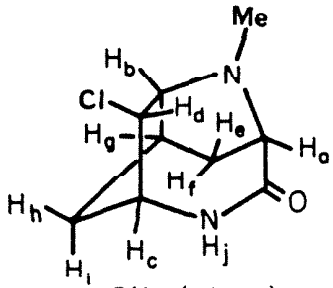


500 NMz ^{1}H NMR Spectrum of 54b and 55 ($CDCl_3$).

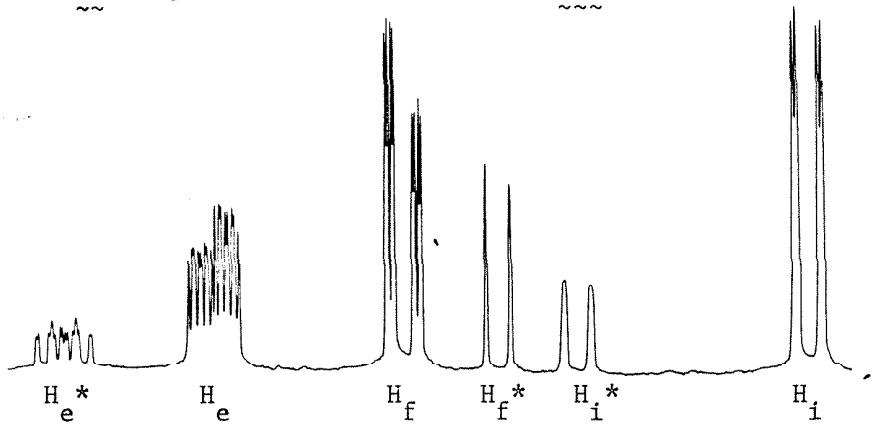
500 MHz ^{1}H NMR Spectrum of 55 and 54b ($CDCl_3$): Expansions.
(NOTE: Protons indicated with asterisk are assigned to 54b)

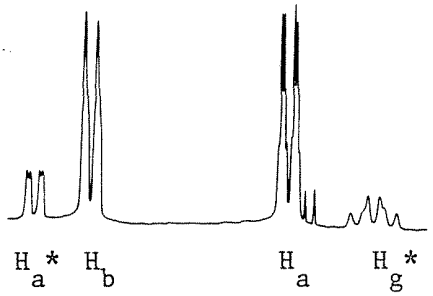


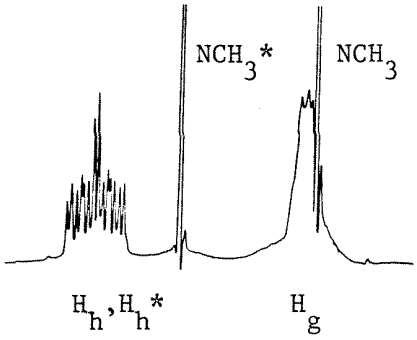
55 (major)

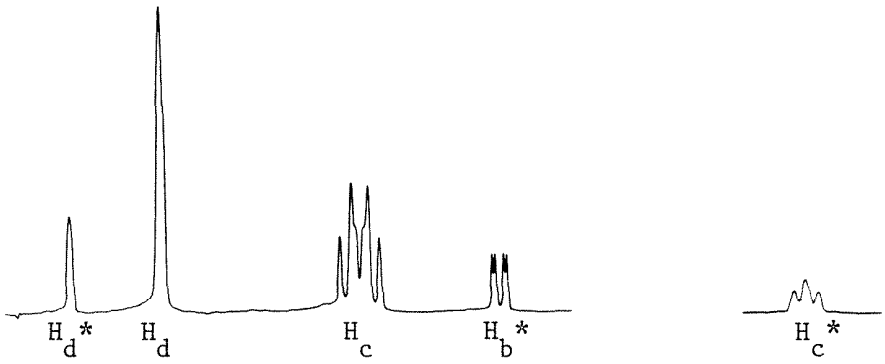


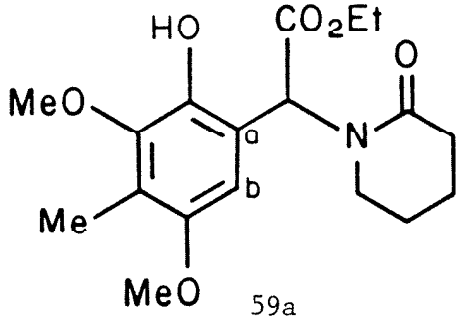
54b (minor)





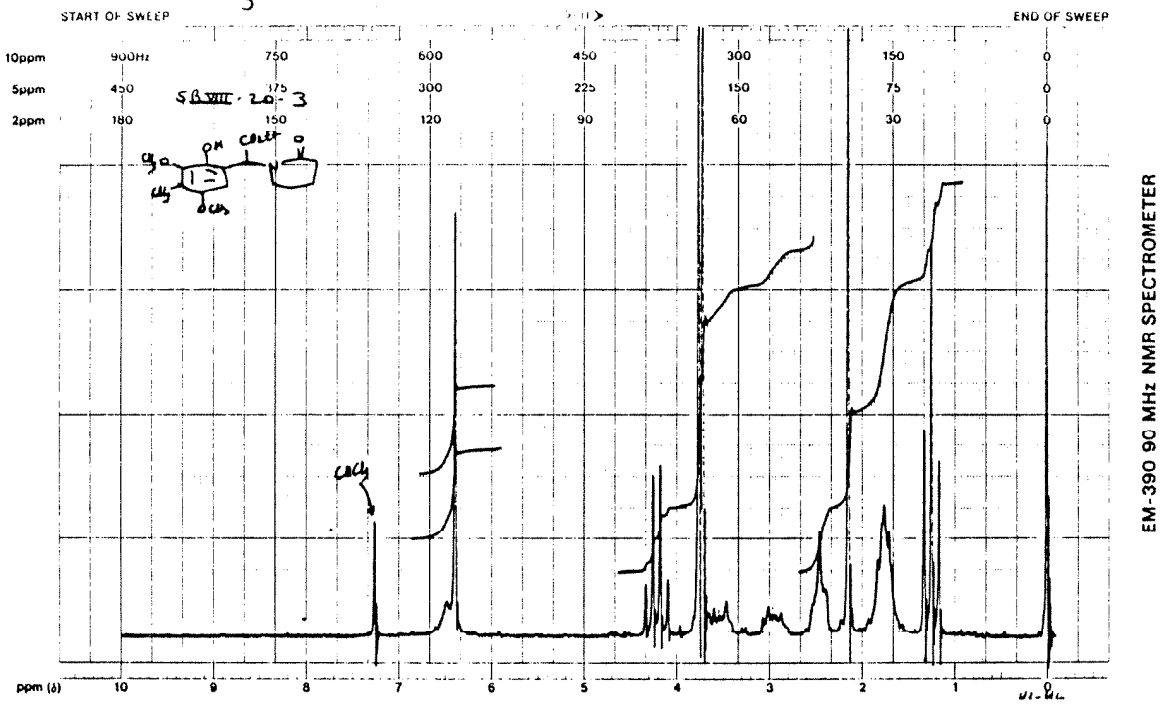




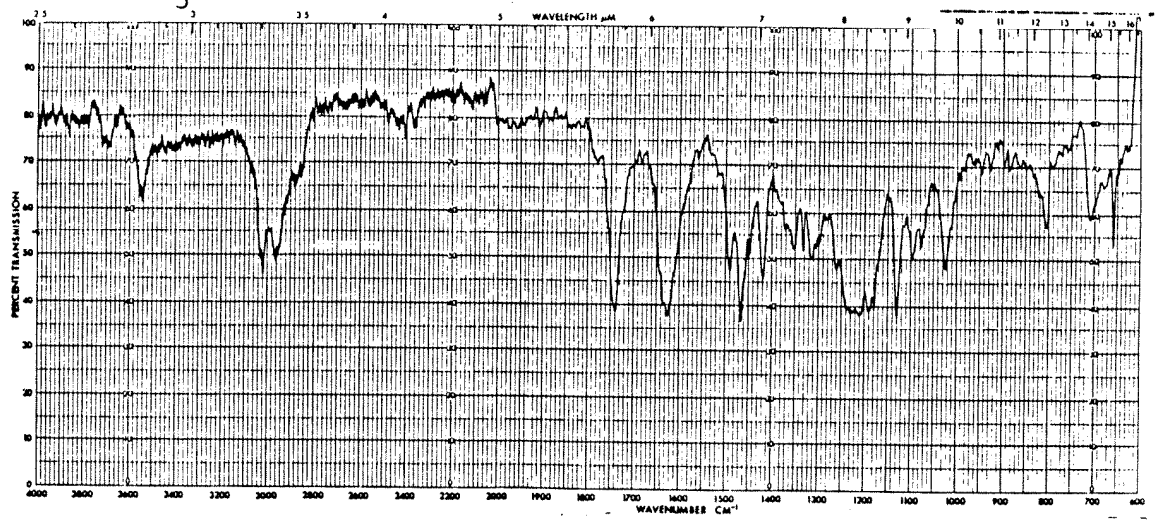


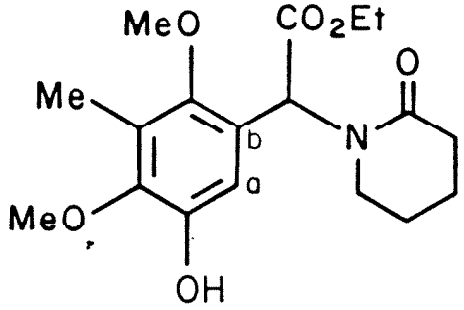
59a

^{1}H NMR ($CDCl_3$)



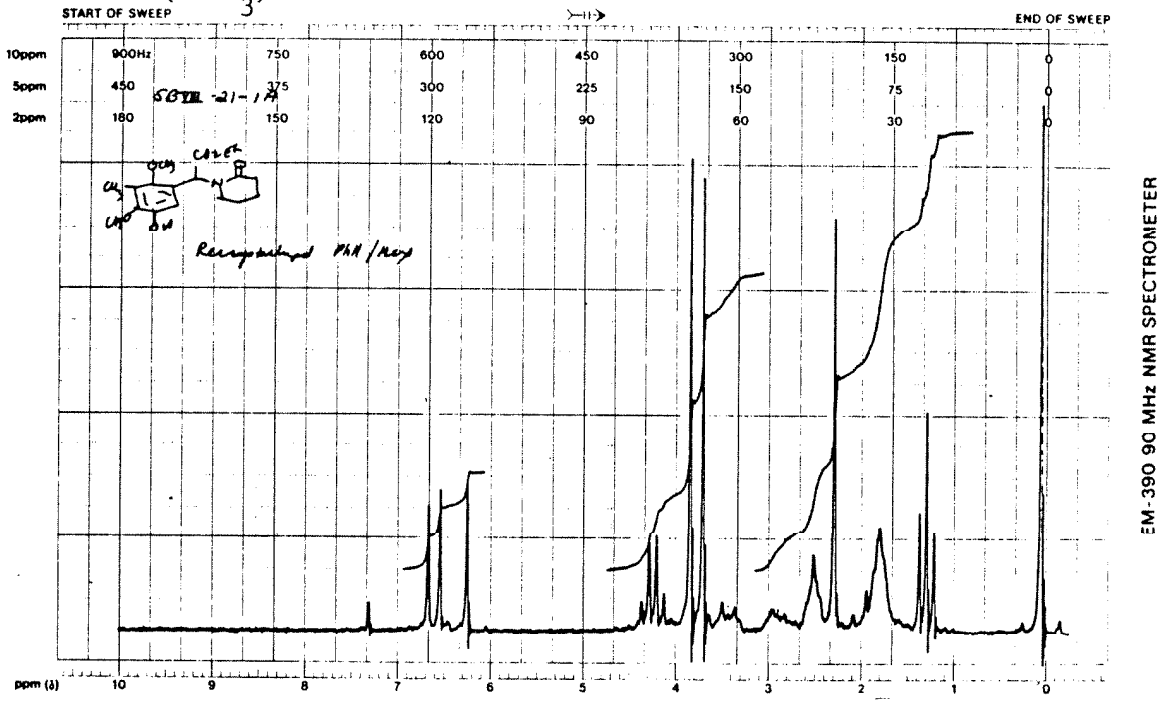
1R ($CHCl_3$)



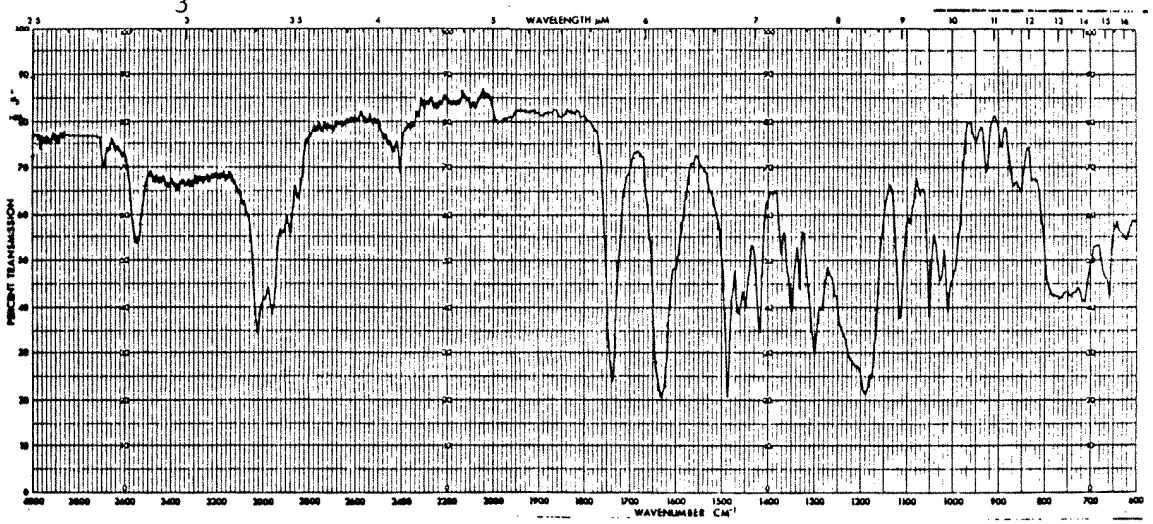


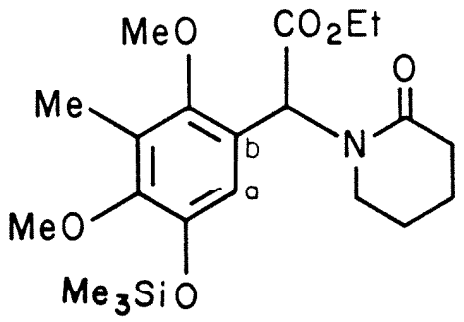
60a

^{1}H NMR ($CDCl_3$)



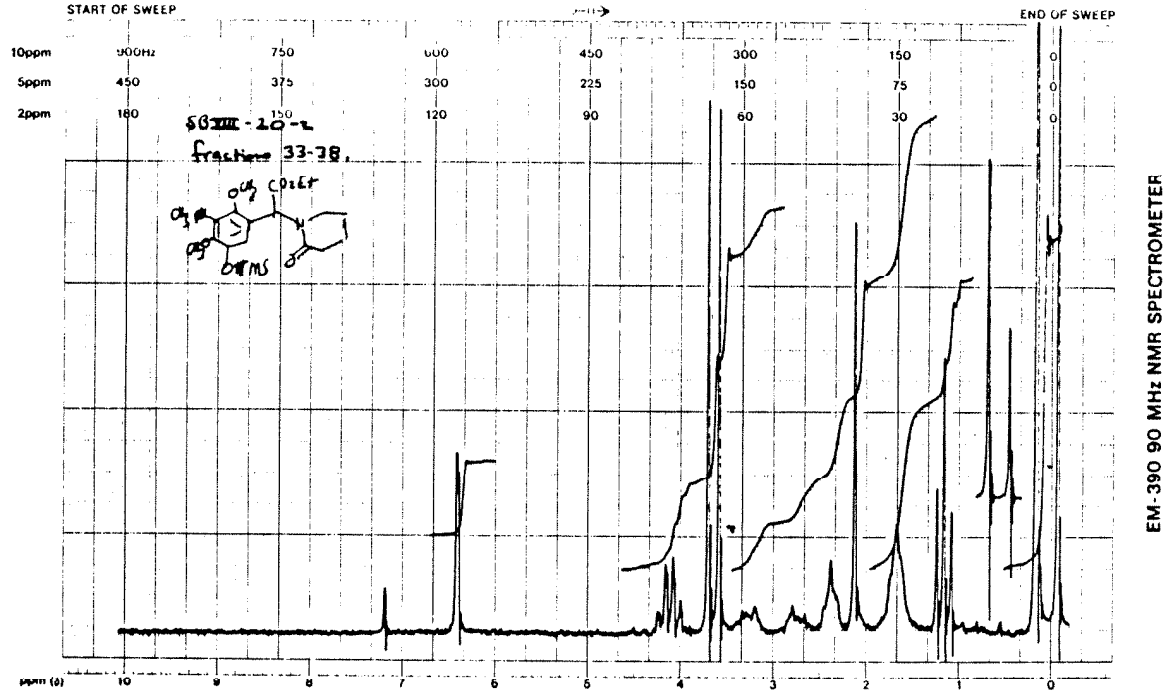
IR ($CHCl_3$)

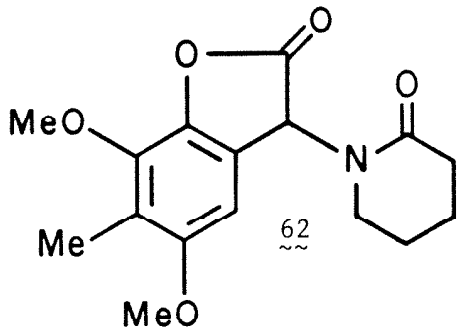




60b

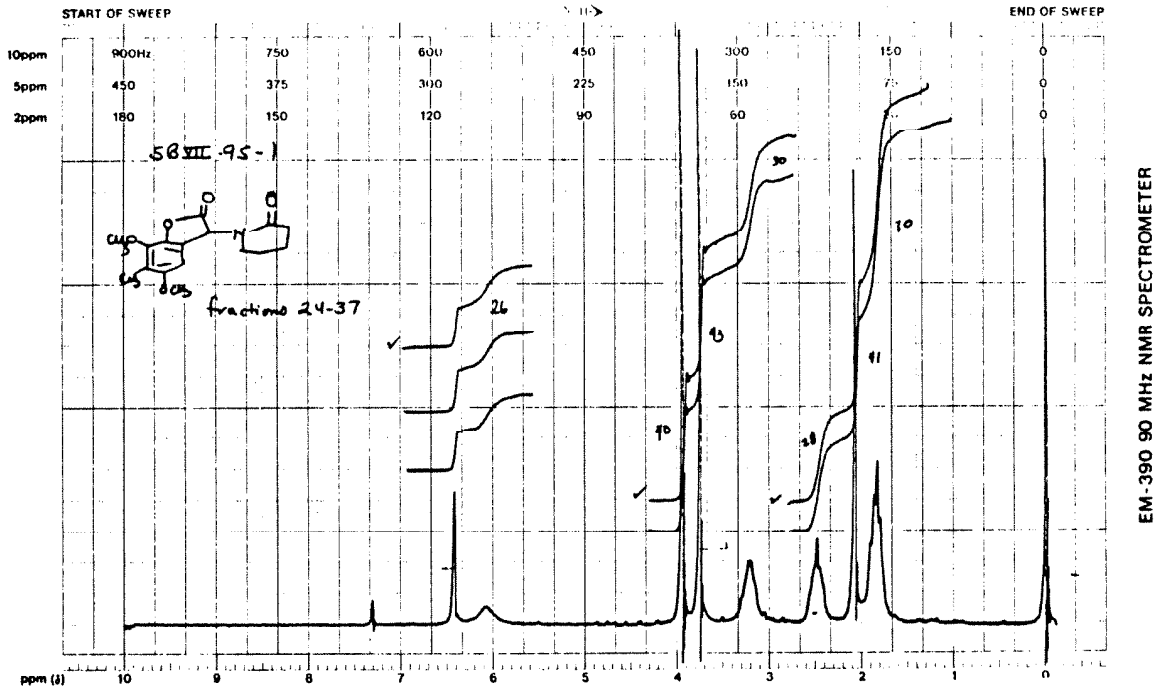
^{1}H NMR ($CDCl_3$)



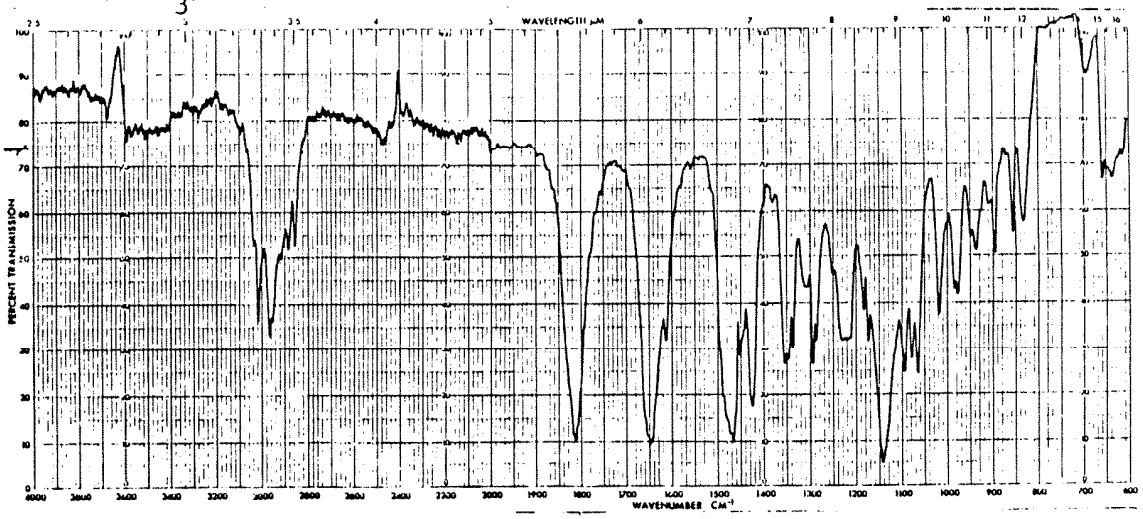


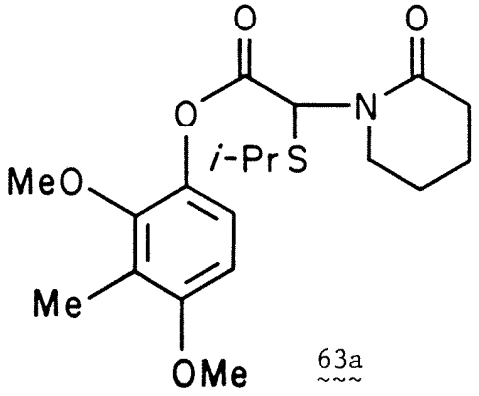
62

^{1}H NMR ($CDCl_3$)



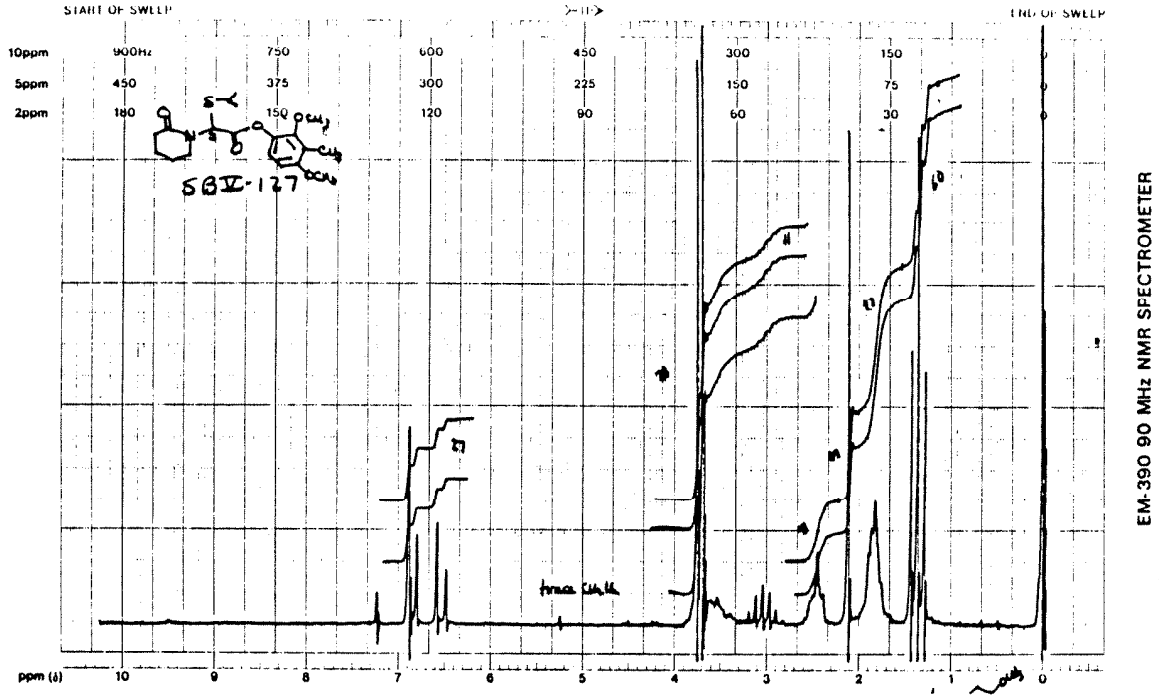
1R ($CHCl_3$)



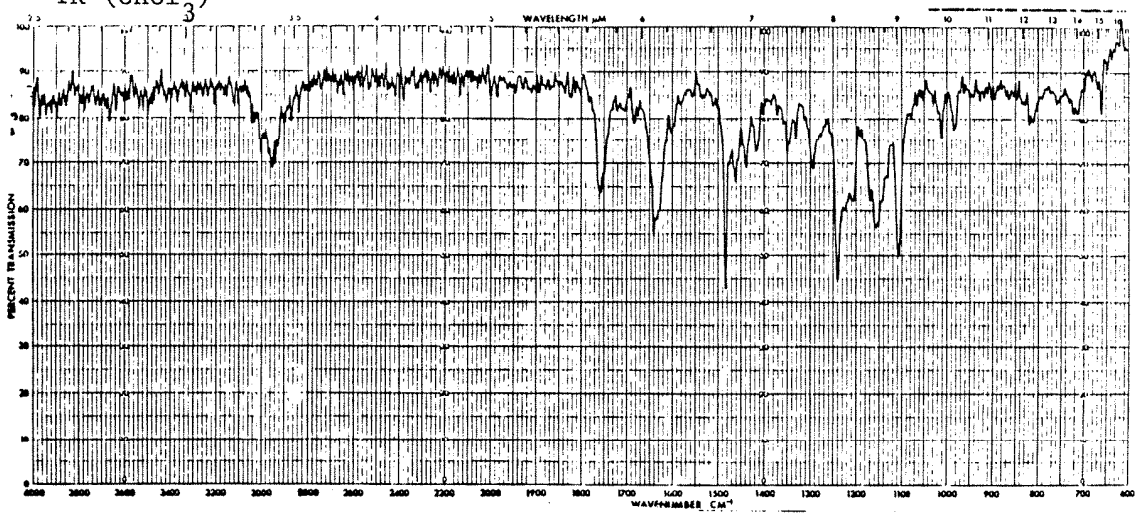


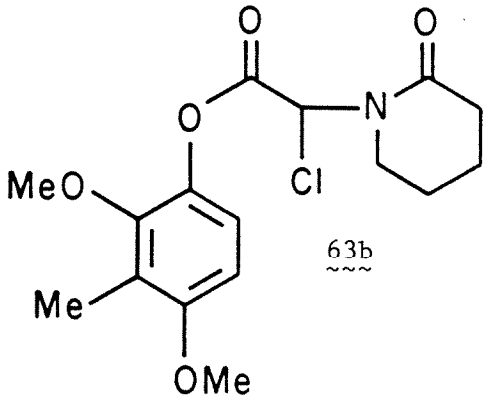
63a

^{1}H NMR ($CDCl_3$)



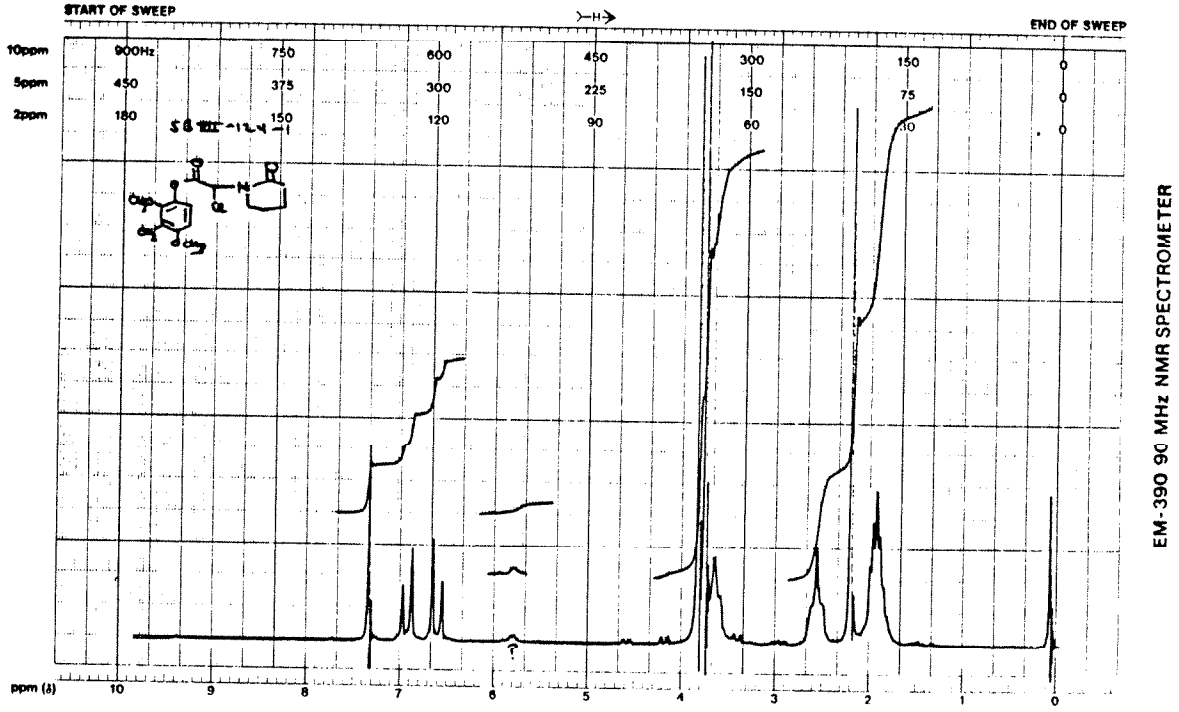
IR ($CHCl_3$)



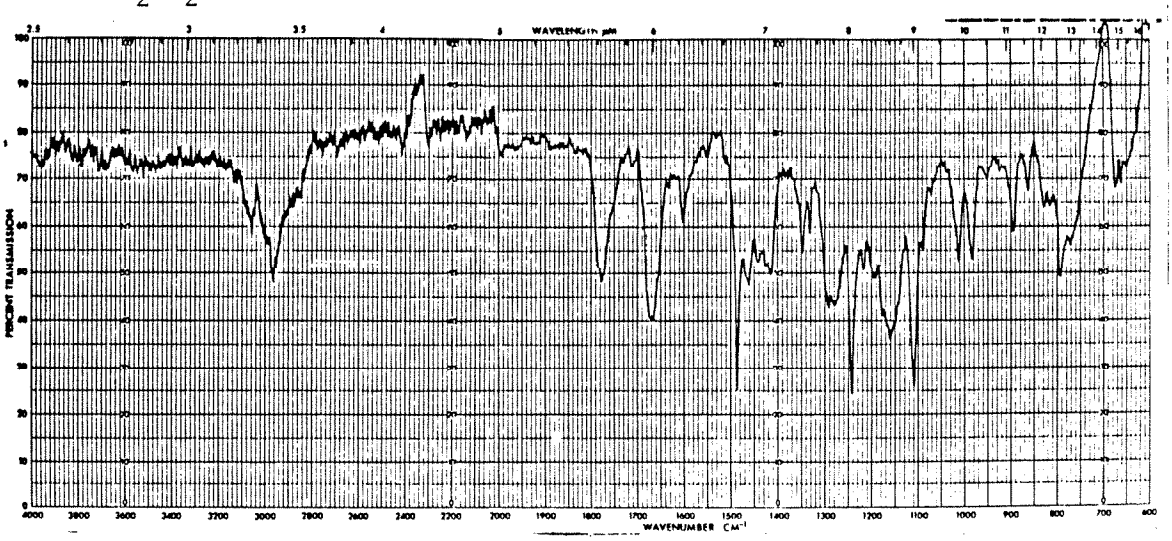


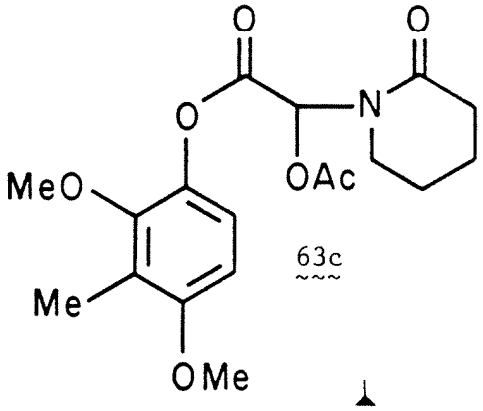
63b

^{1}H NMR ($CDCl_3$)



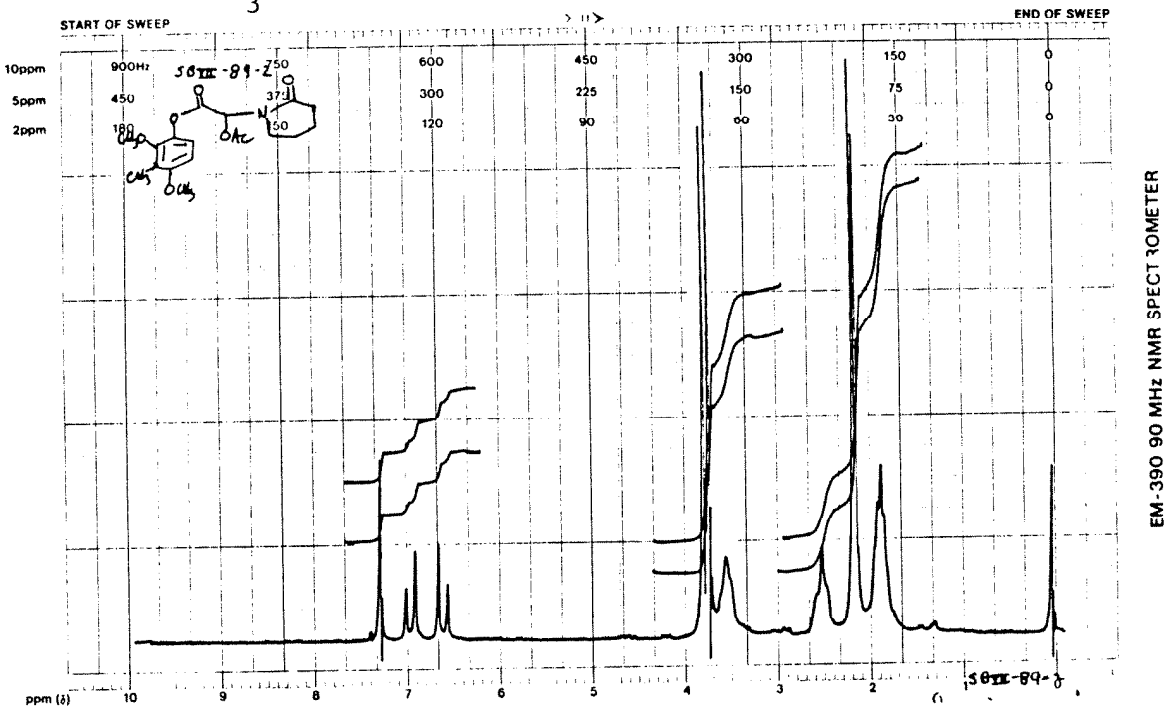
1R (CH_2Cl_2)



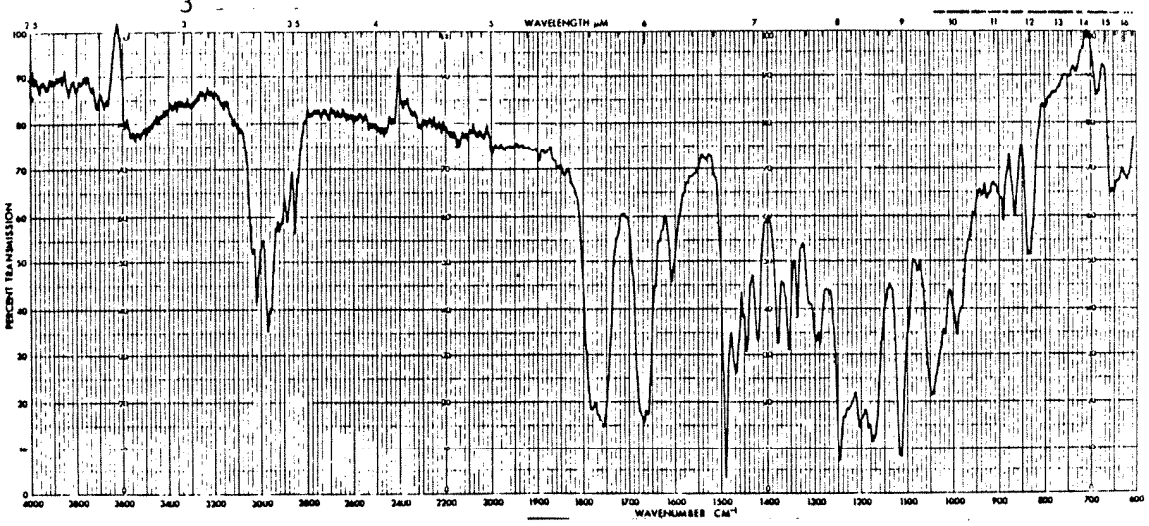


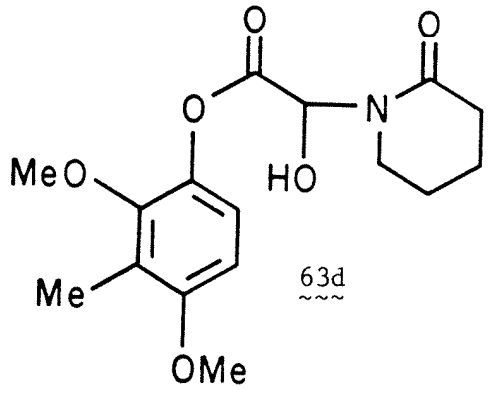
63c

^{1}H NMR ($CDCl_3$)



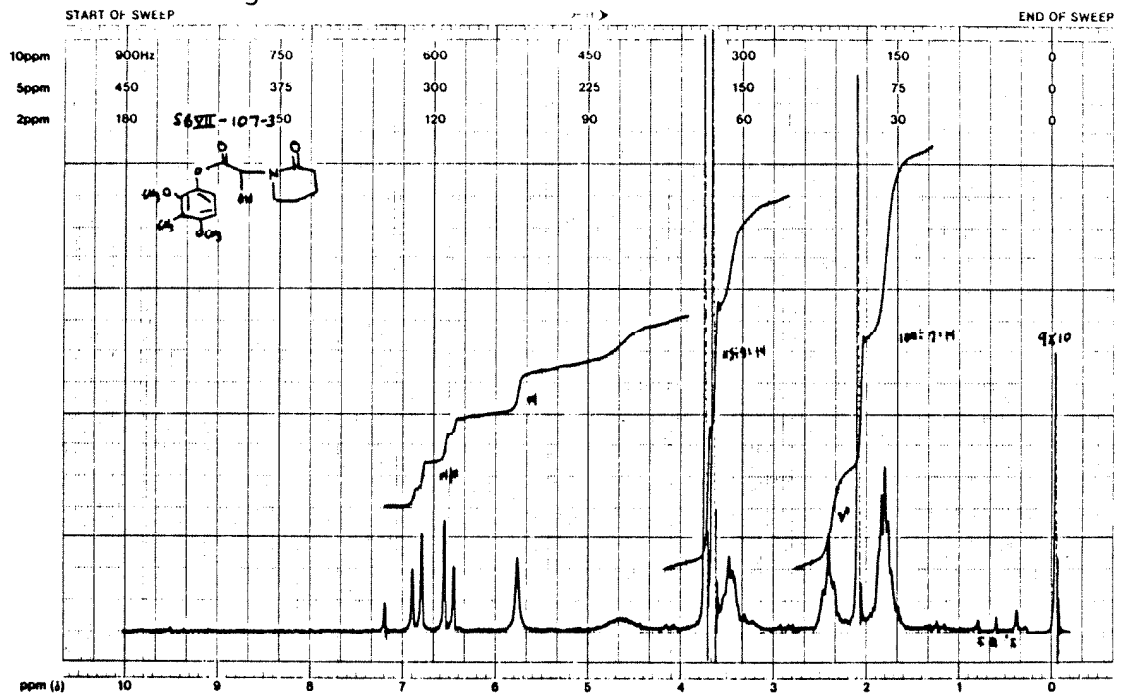
1R ($CHCl_3$)



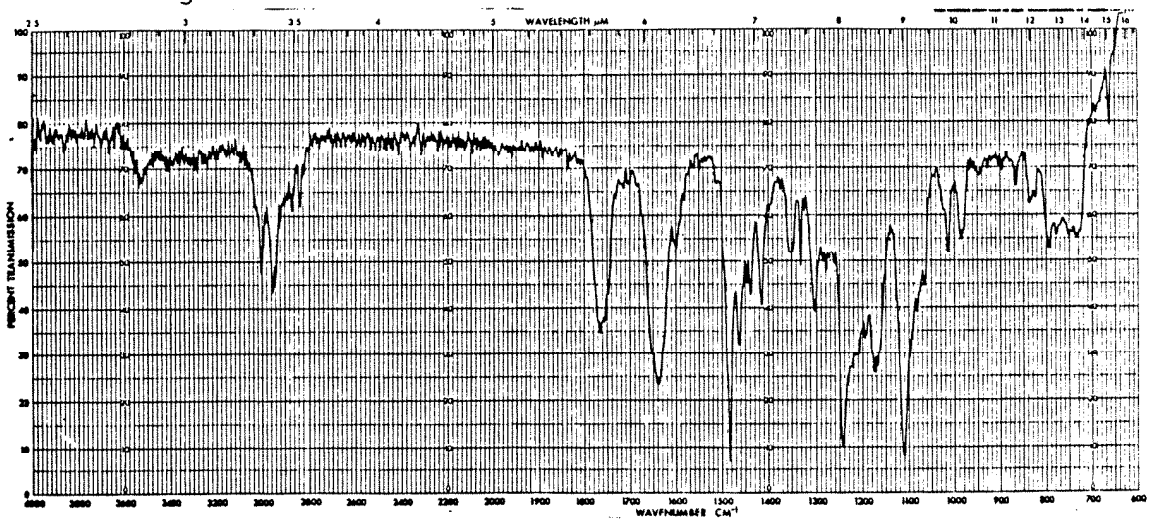


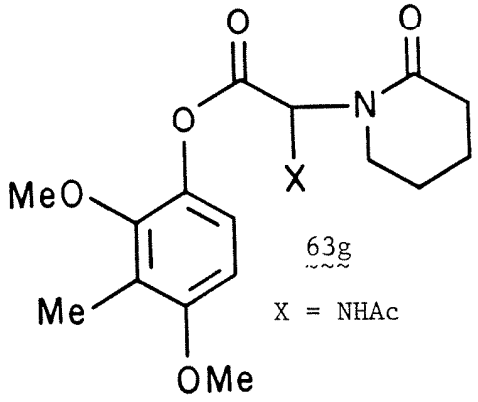
63d

^{1}H NMR ($CDCl_3$)



IR ($CHCl_3$)

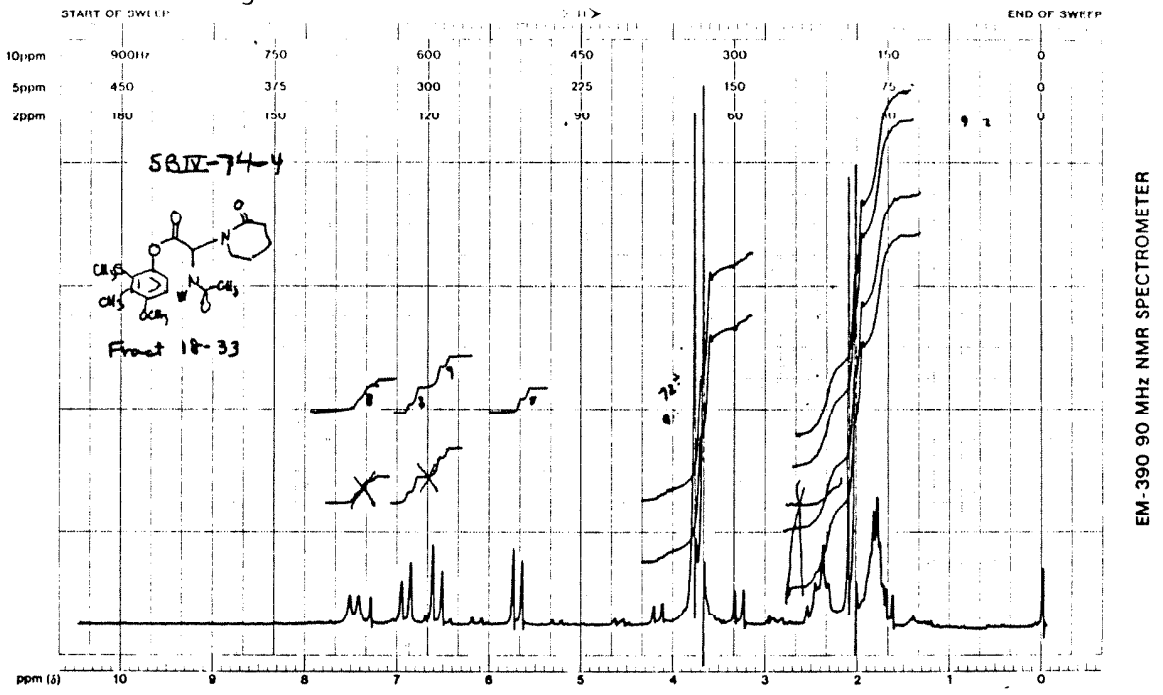




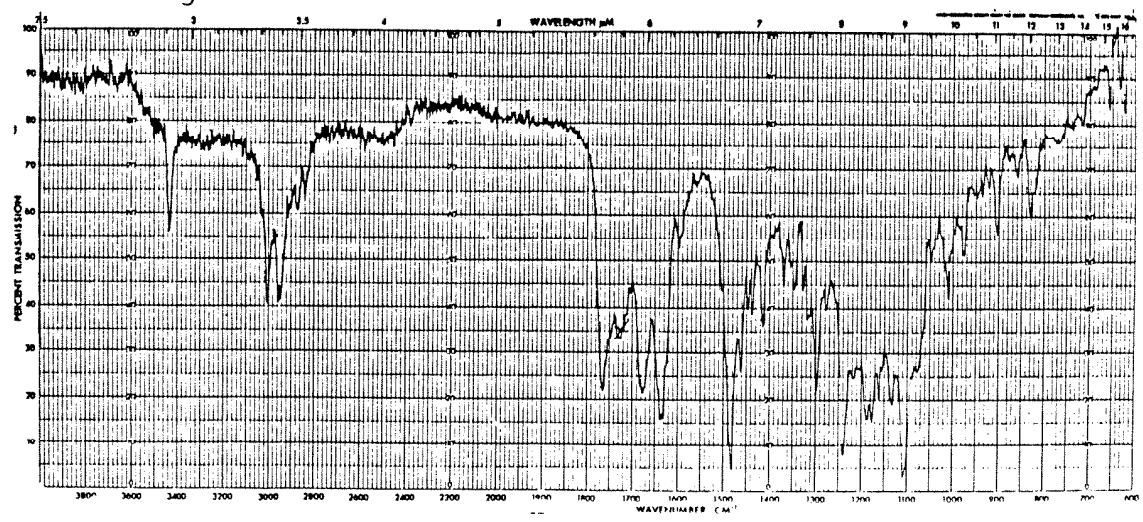
63g

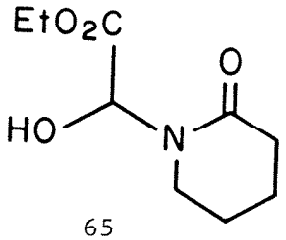
X = NHAc

^{1}H NMR ($CDCl_3$)



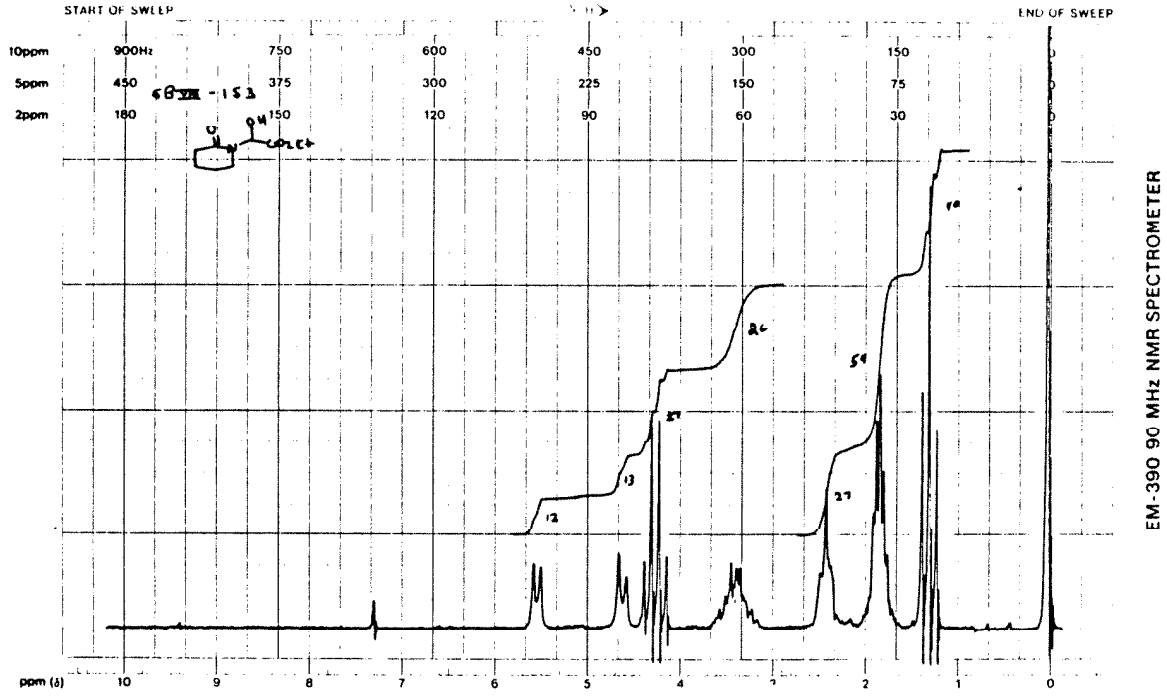
IR ($CHCl_3$)



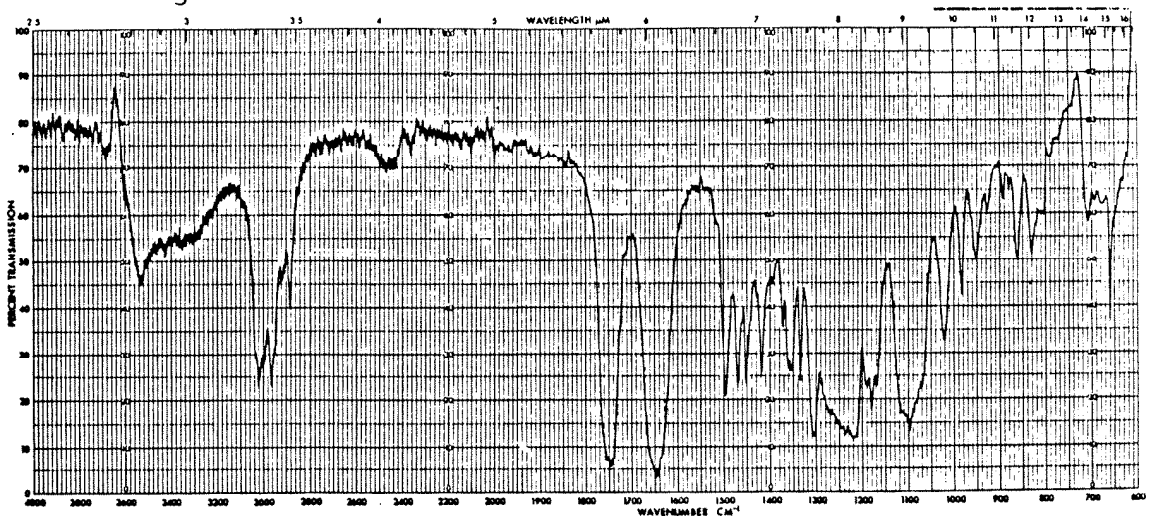


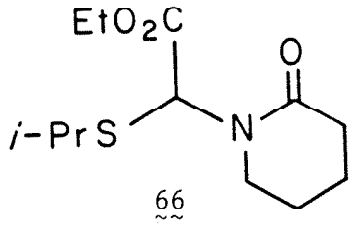
65

^{1}H NMR ($CDCl_3$)



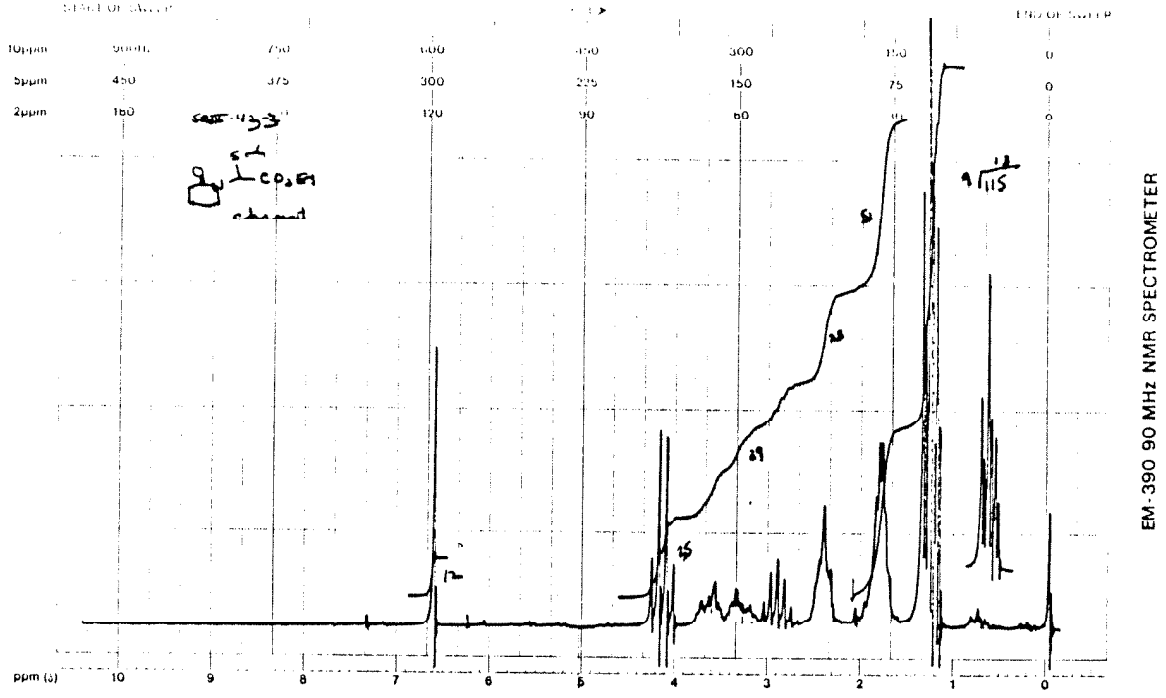
1R ($CHCl_3$)



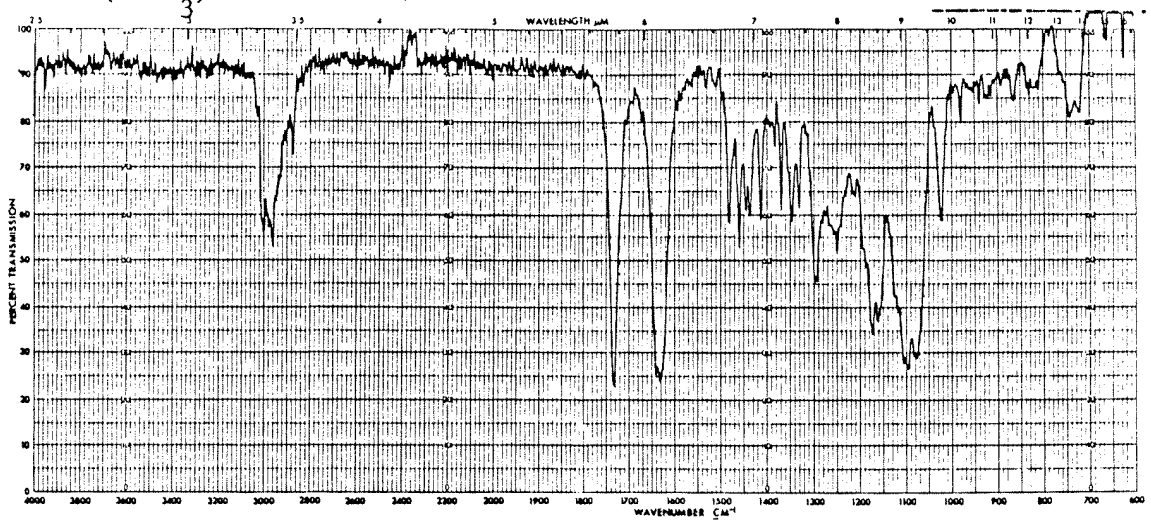


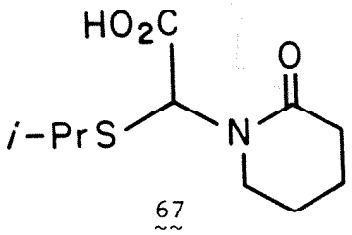
66

^{1}H NMR ($CDCl_3$)



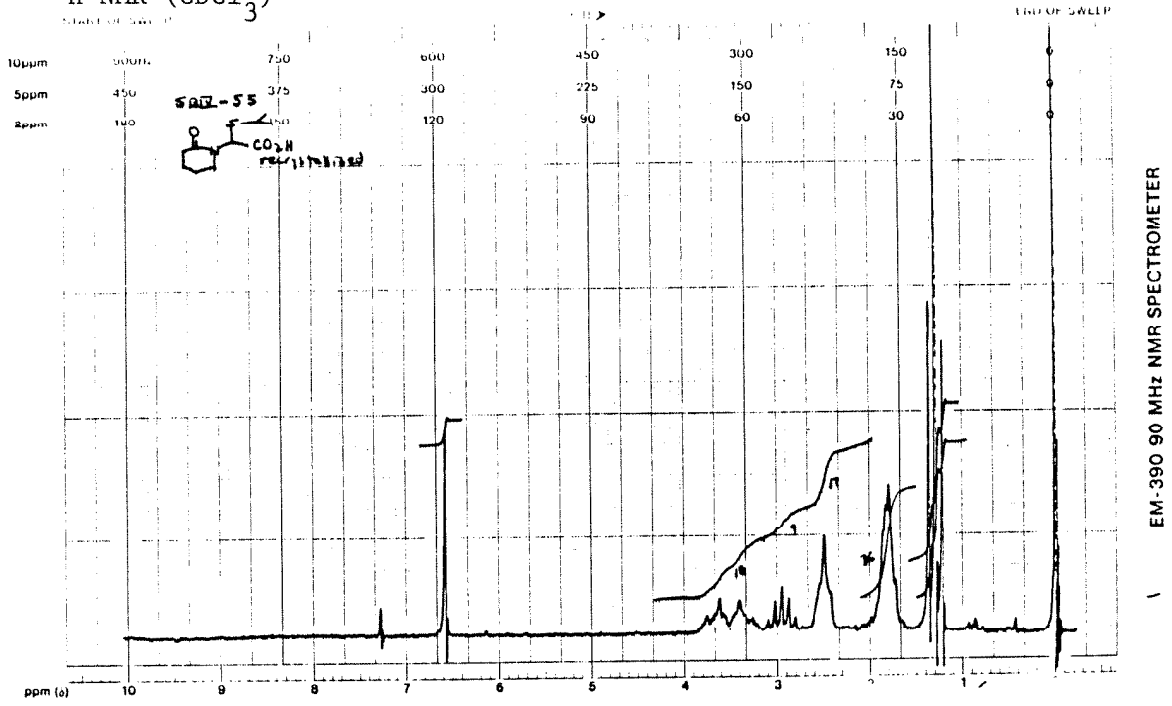
IR ($CHCl_3$)



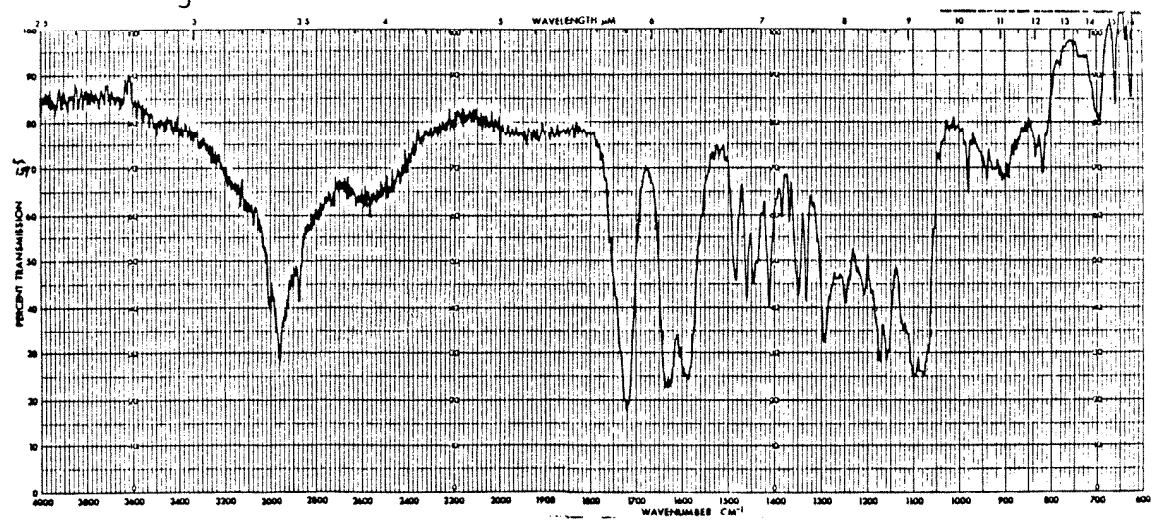


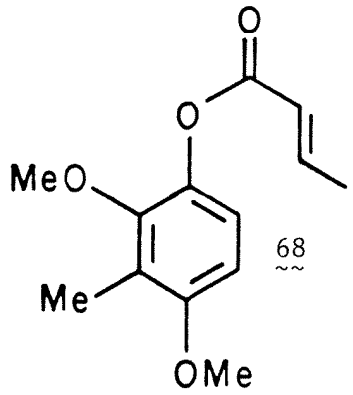
67

^{1}H NMR ($CDCl_3$)



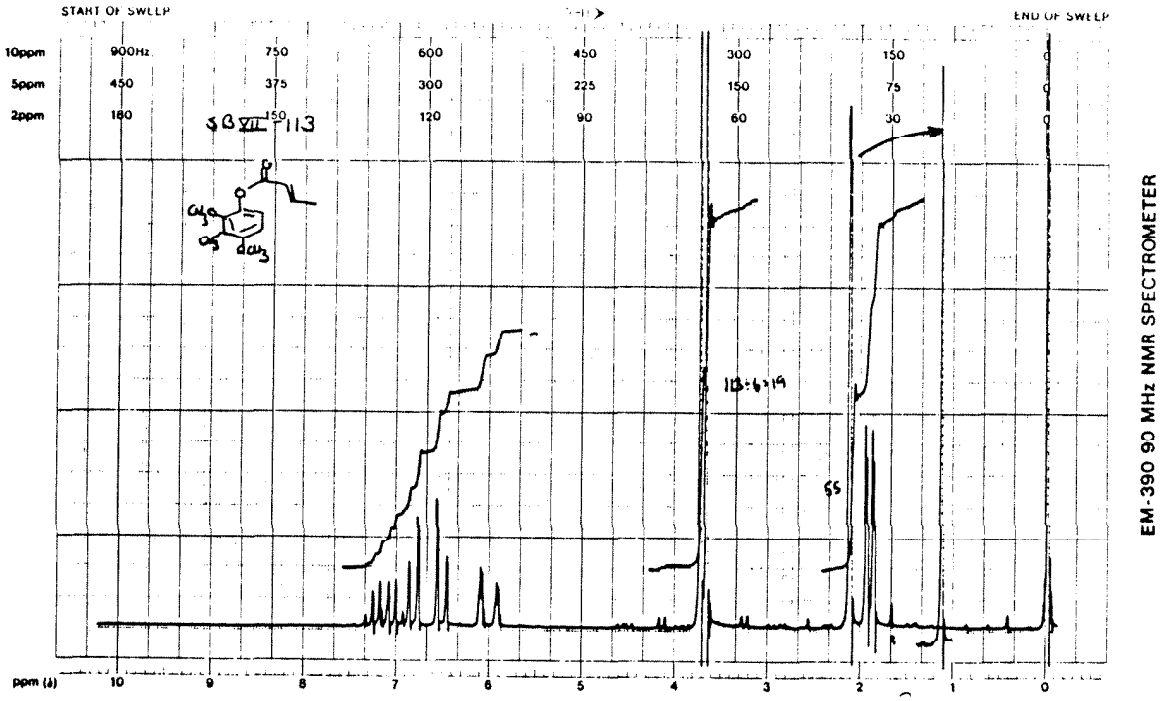
IR ($CHCl_3$)



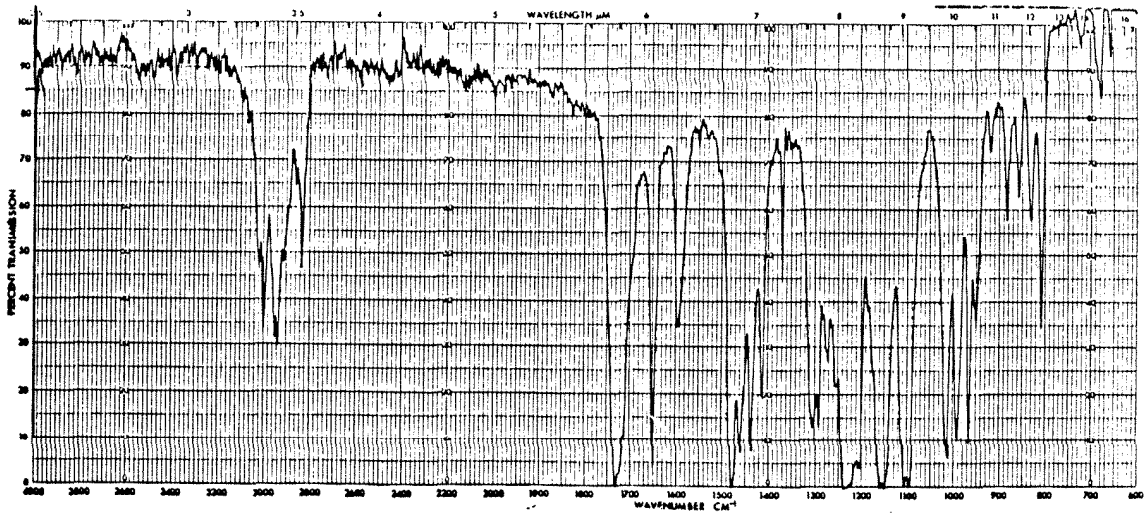


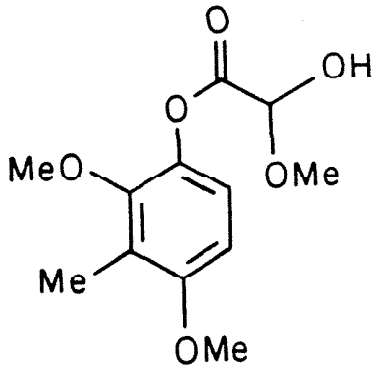
68

^{1}H NMR ($CDCl_3$)



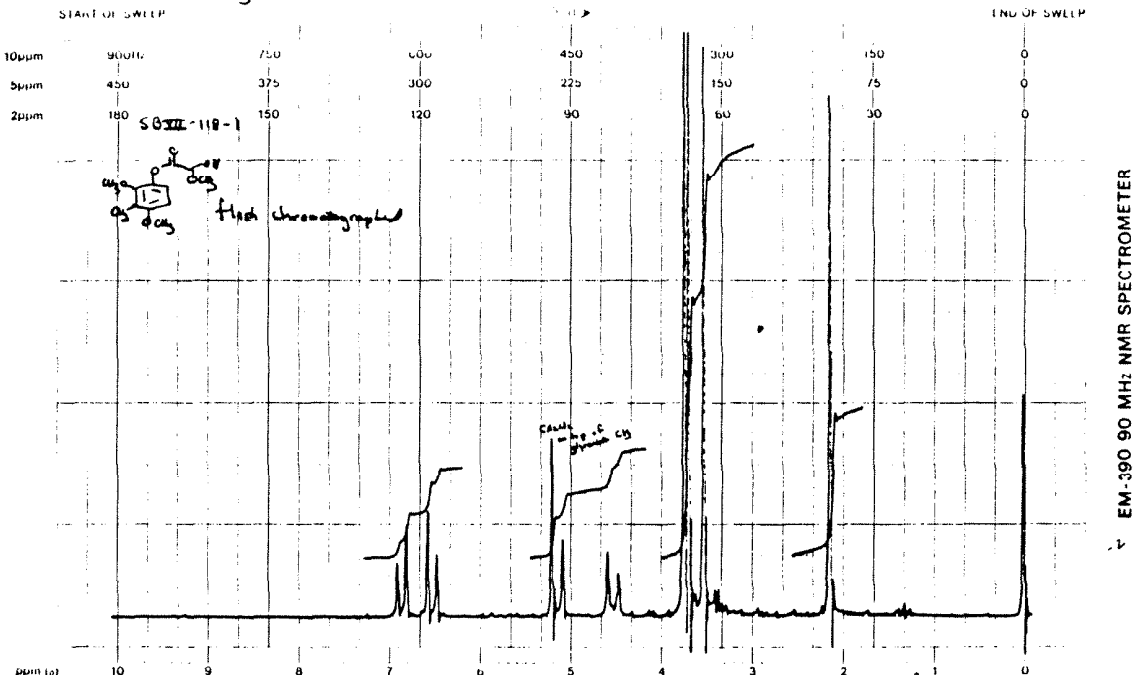
1R ($CHCl_3$)

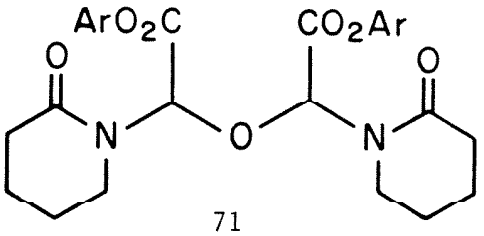




69

^{1}H NMR ($CDCl_3$)

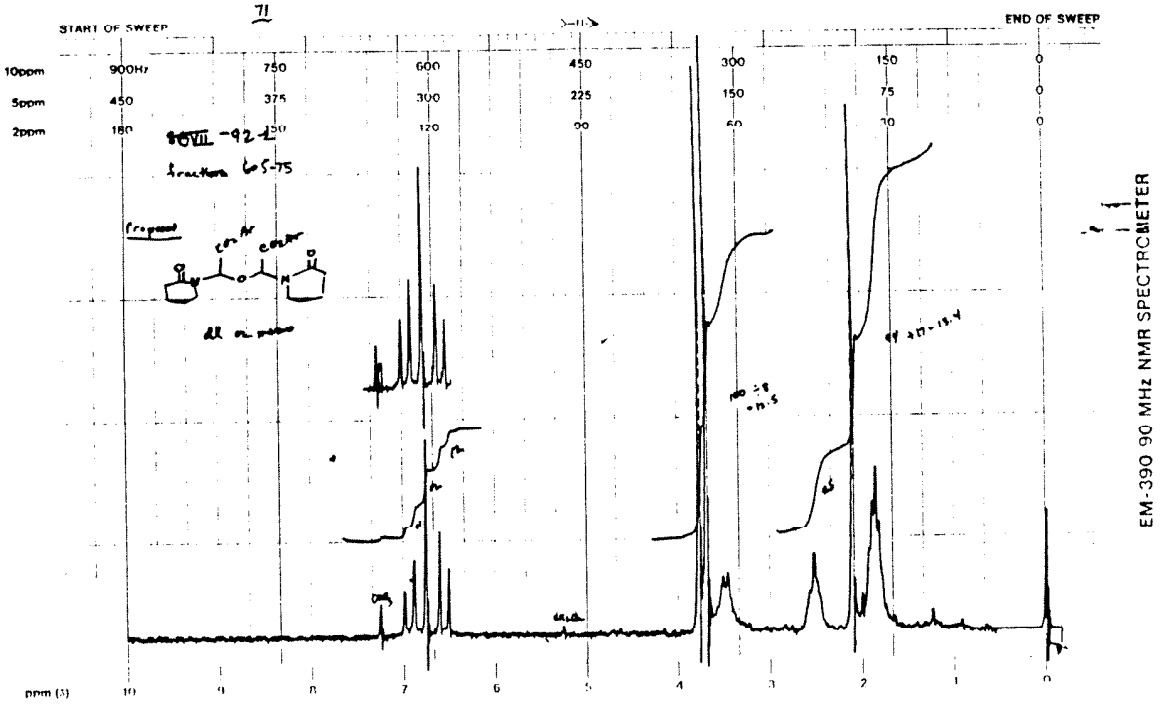




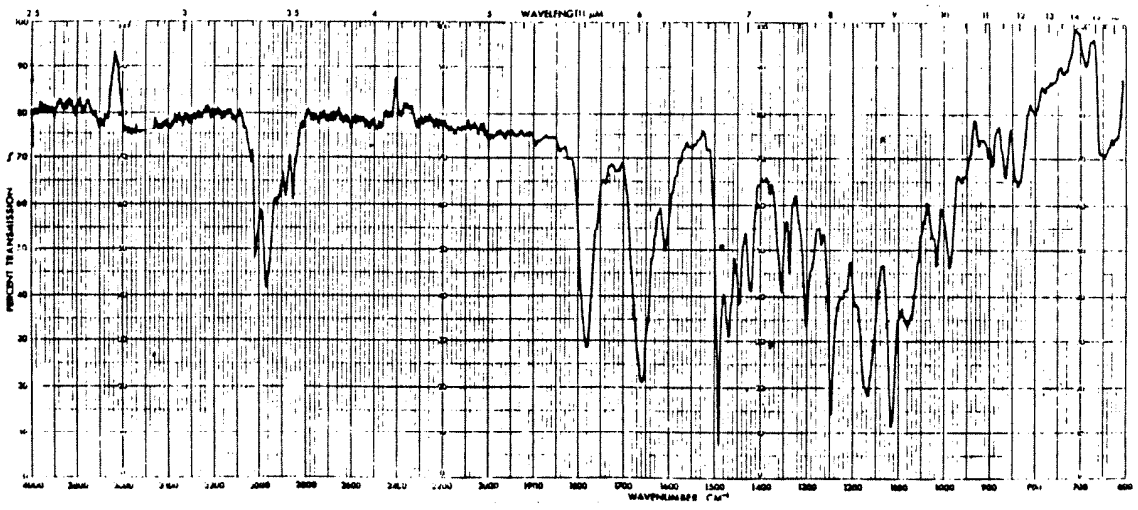
71

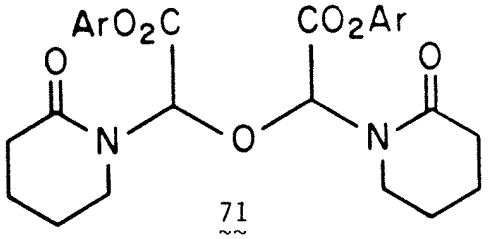
d,l or meso

^{1}H NMR ($CDCl_3$)



IR ($CHCl_3$)

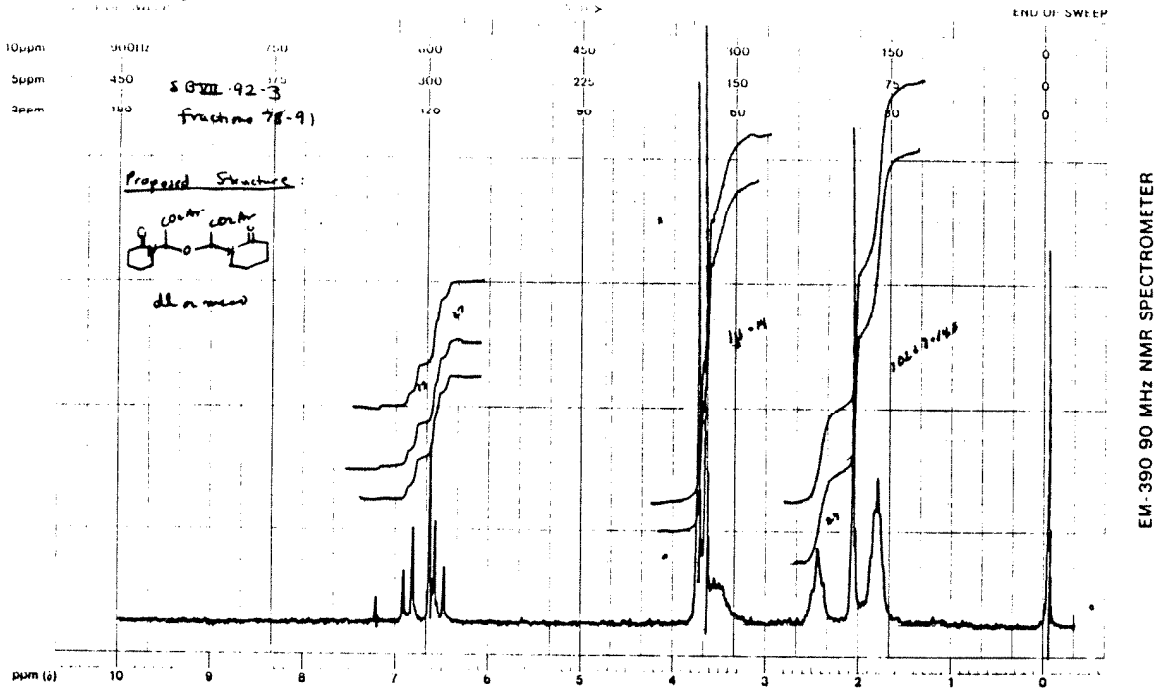




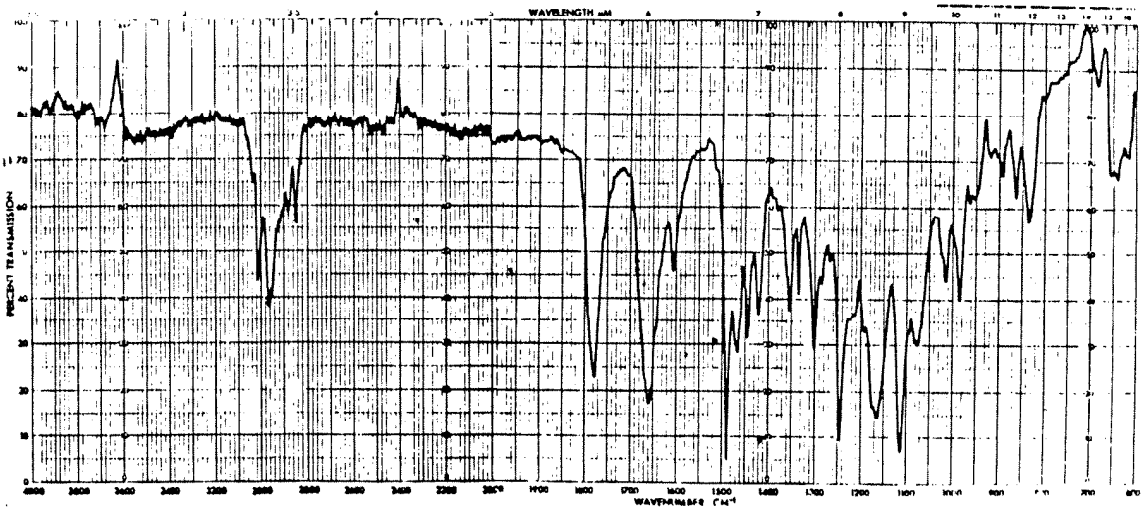
71

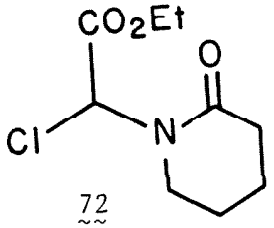
d,l or meso

^{1}H NMR ($CDCl_3$)



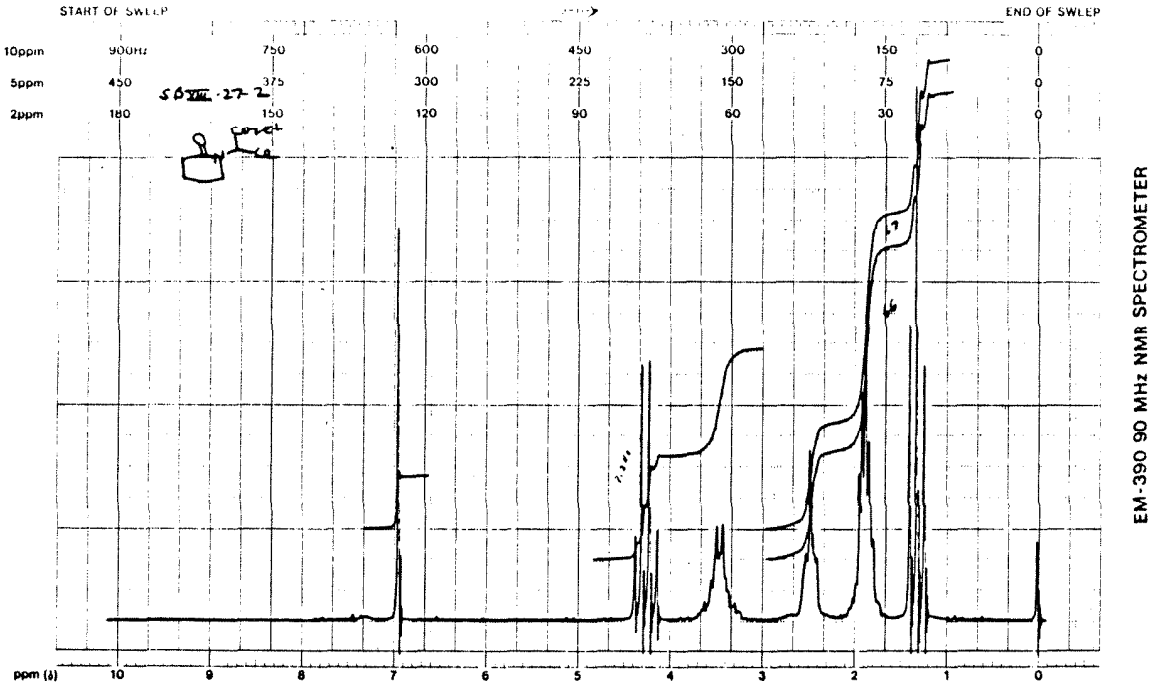
IR ($CHCl_3$)



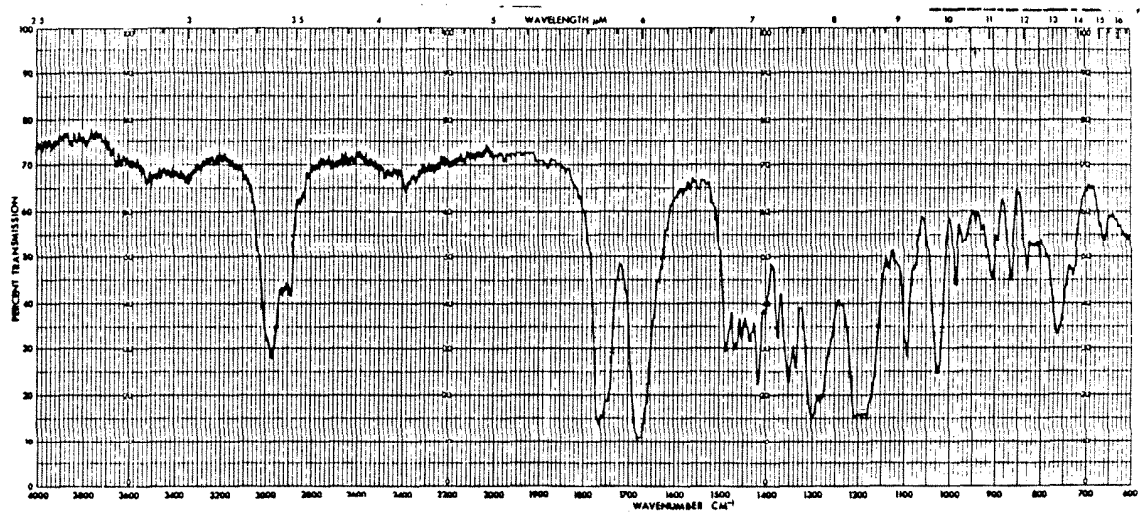


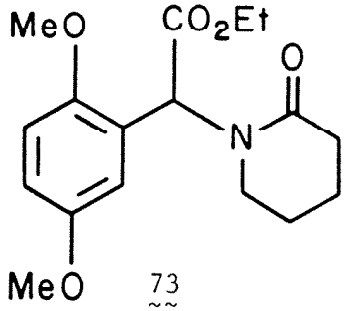
72

^{1}H NMR ($CDCl_3$)



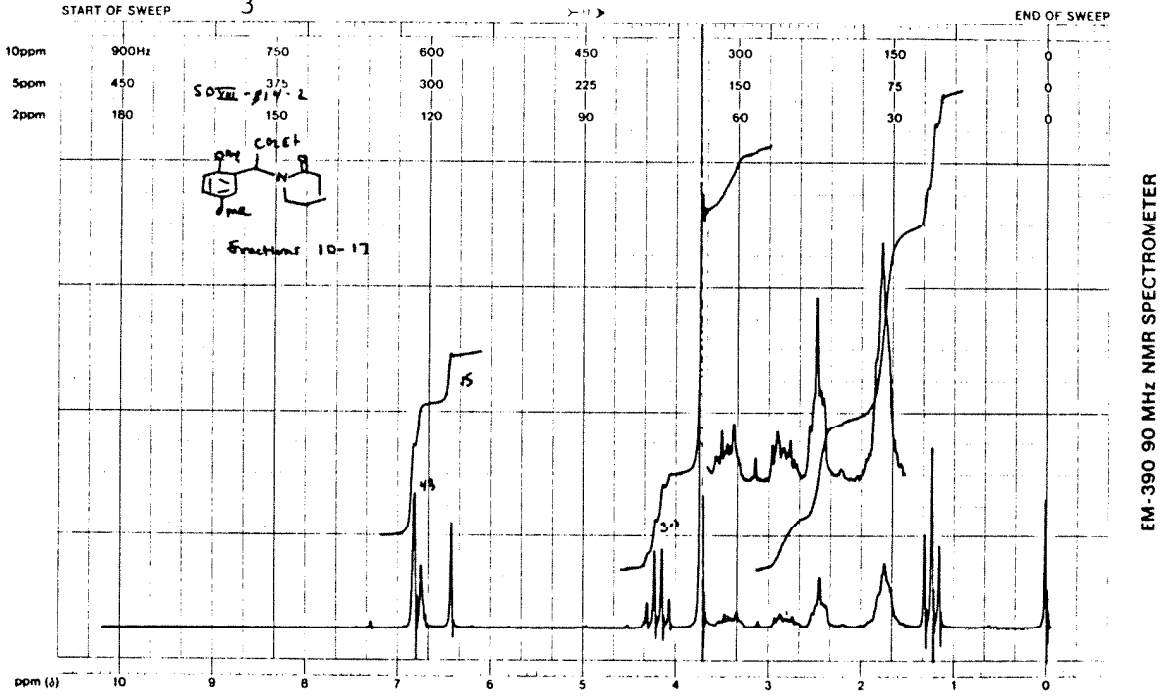
IR (neat)



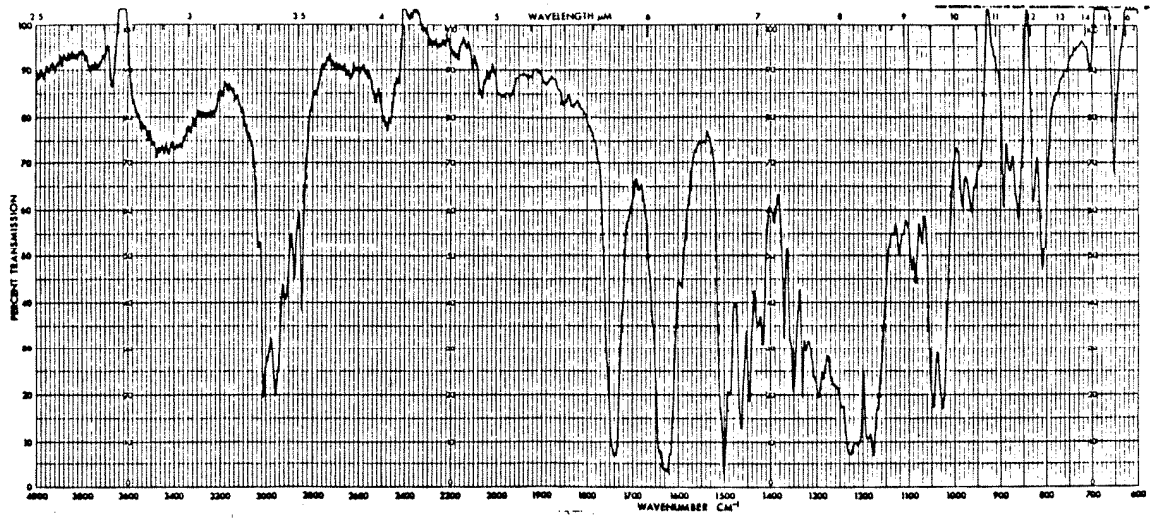


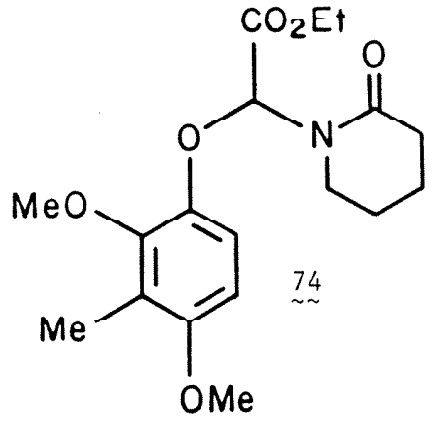
73

^{1}H NMR ($CDCl_3$)



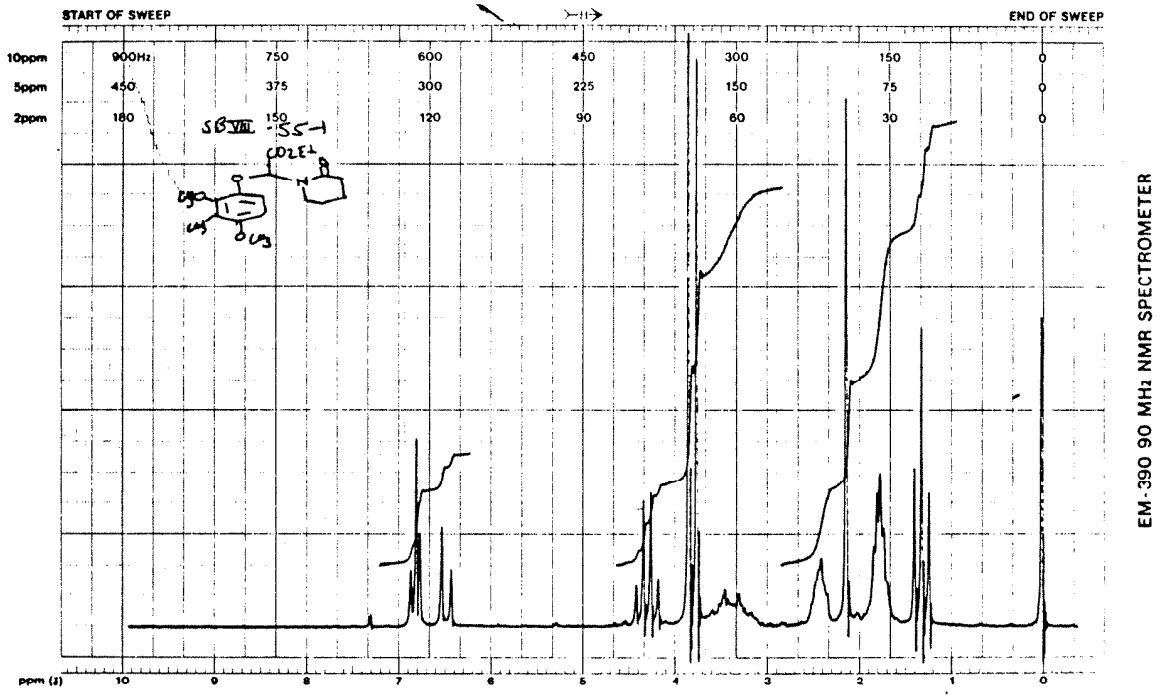
IR ($CHCl_3$)



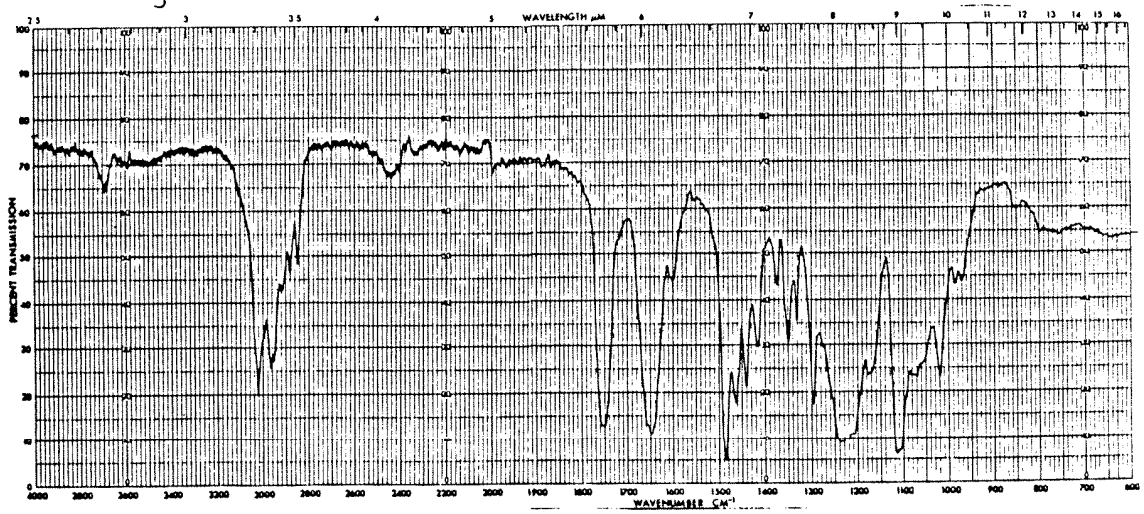


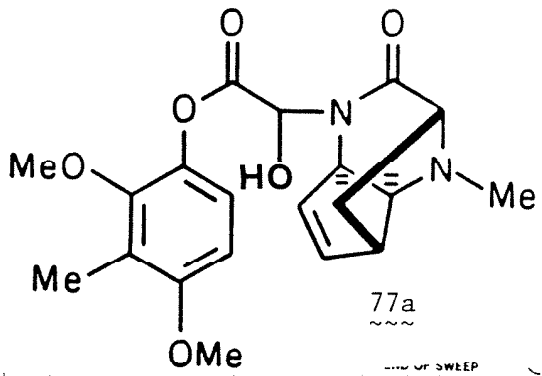
74

^{1}H NMR ($CDCl_3$)



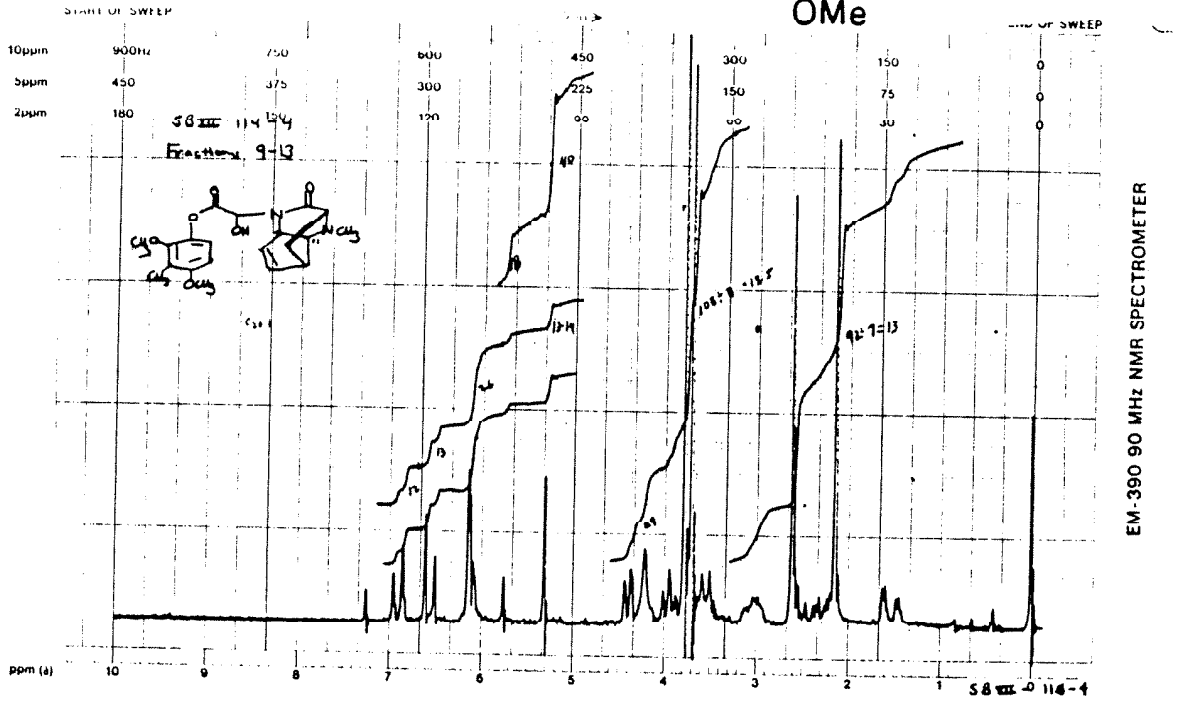
IR ($CHCl_3$)



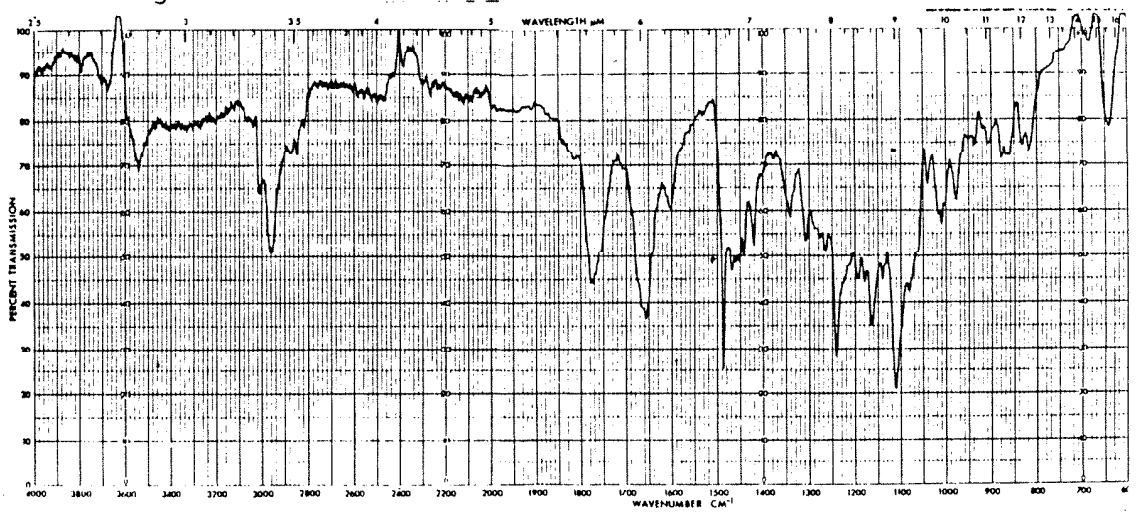


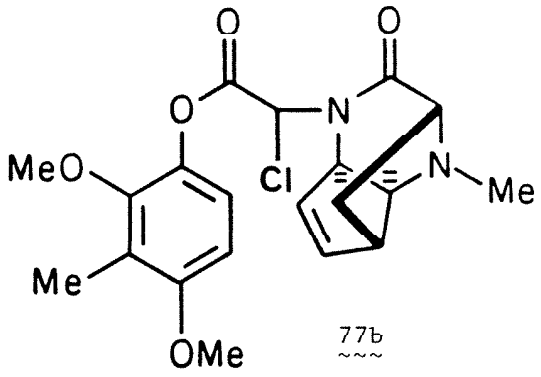
77a

^{1}H NMR ($CDCl_3$)



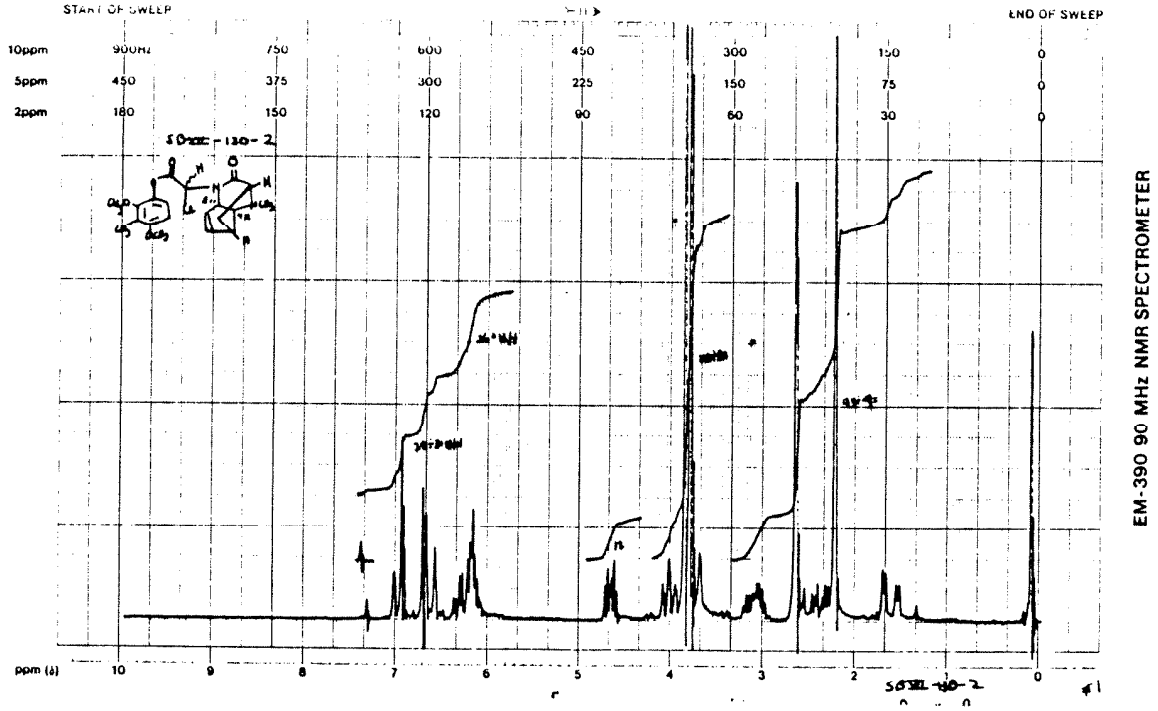
IR ($CHCl_3$)

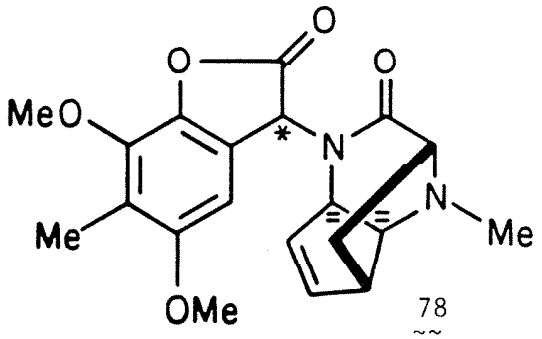




77b

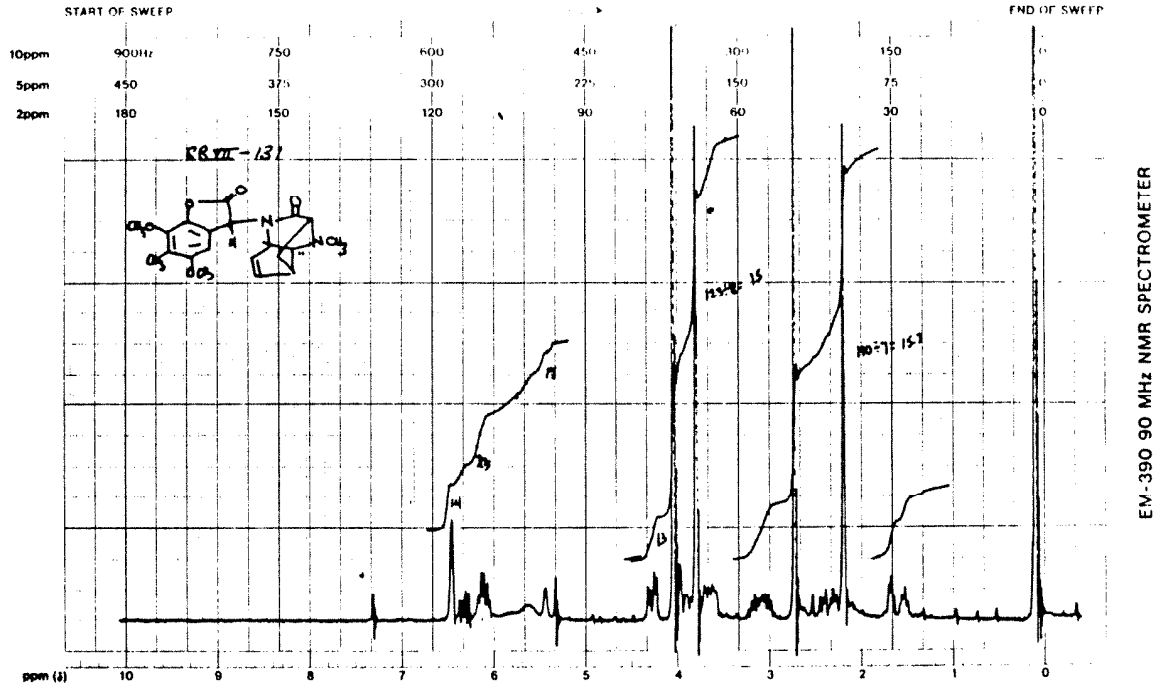
^{1}H NMR ($CDCl_3$)



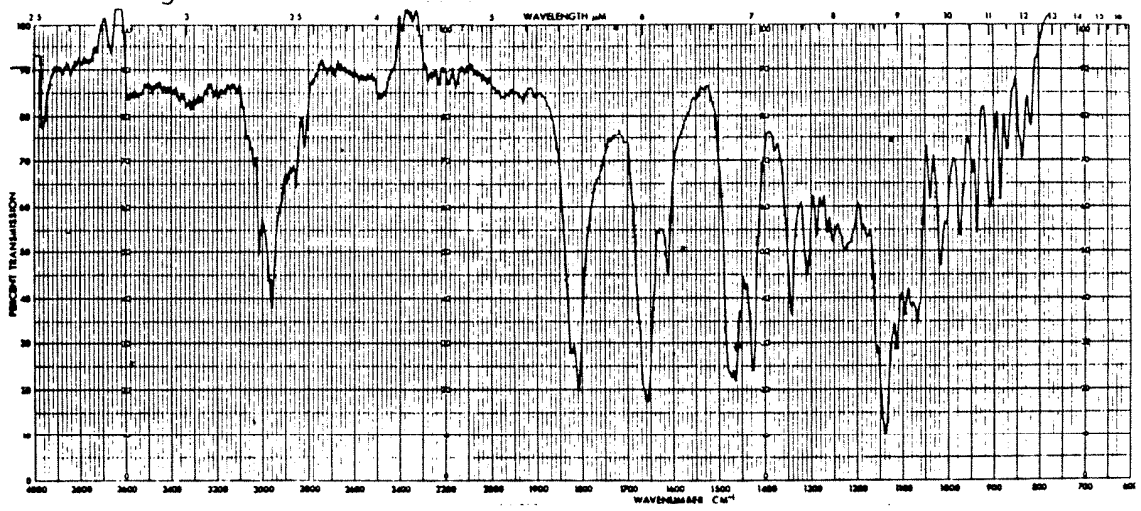


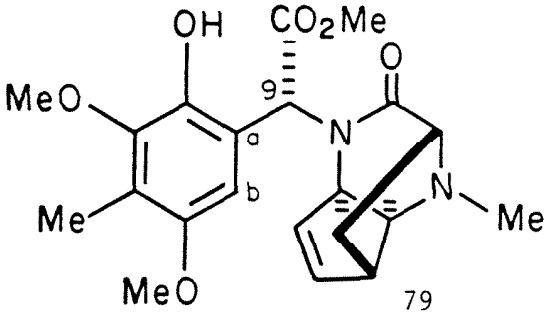
78

^{1}H NMR ($CDCl_3$)



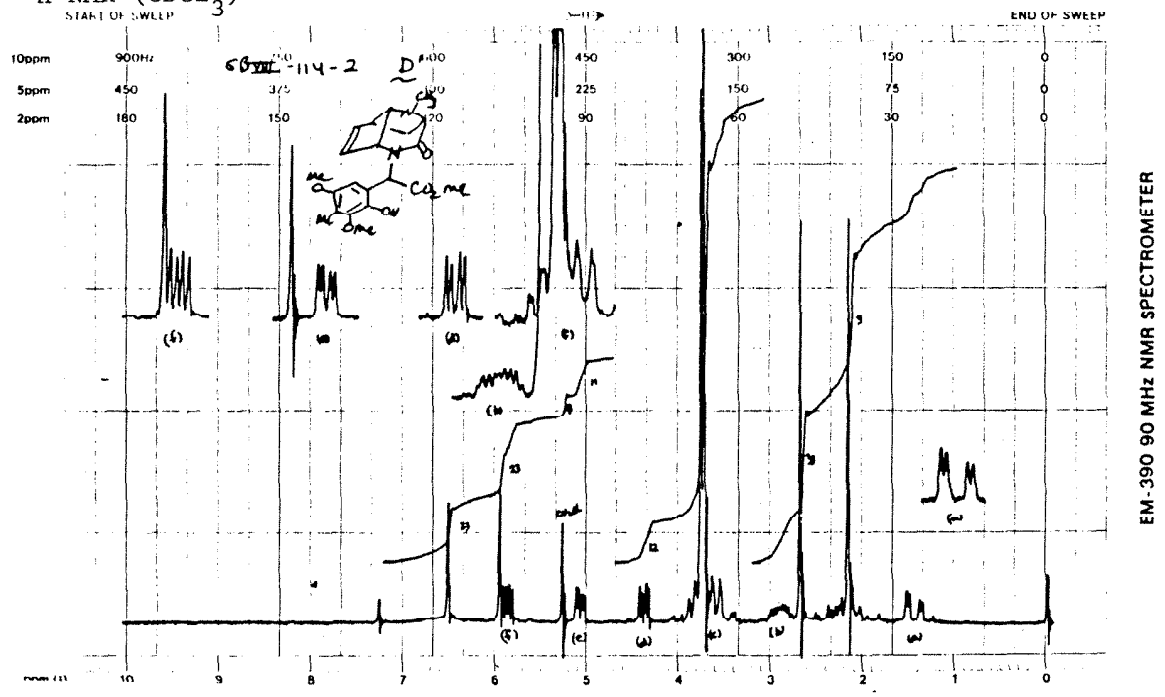
IR ($CHCl_3$)



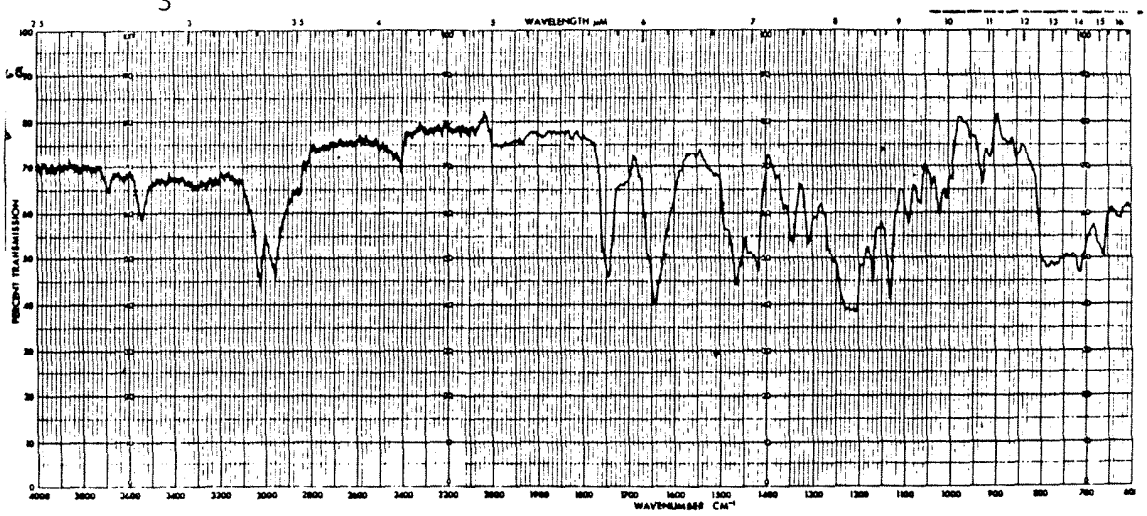


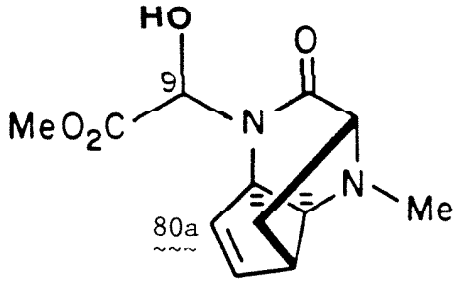
79

^{1}H NMR ($CDCl_3$)



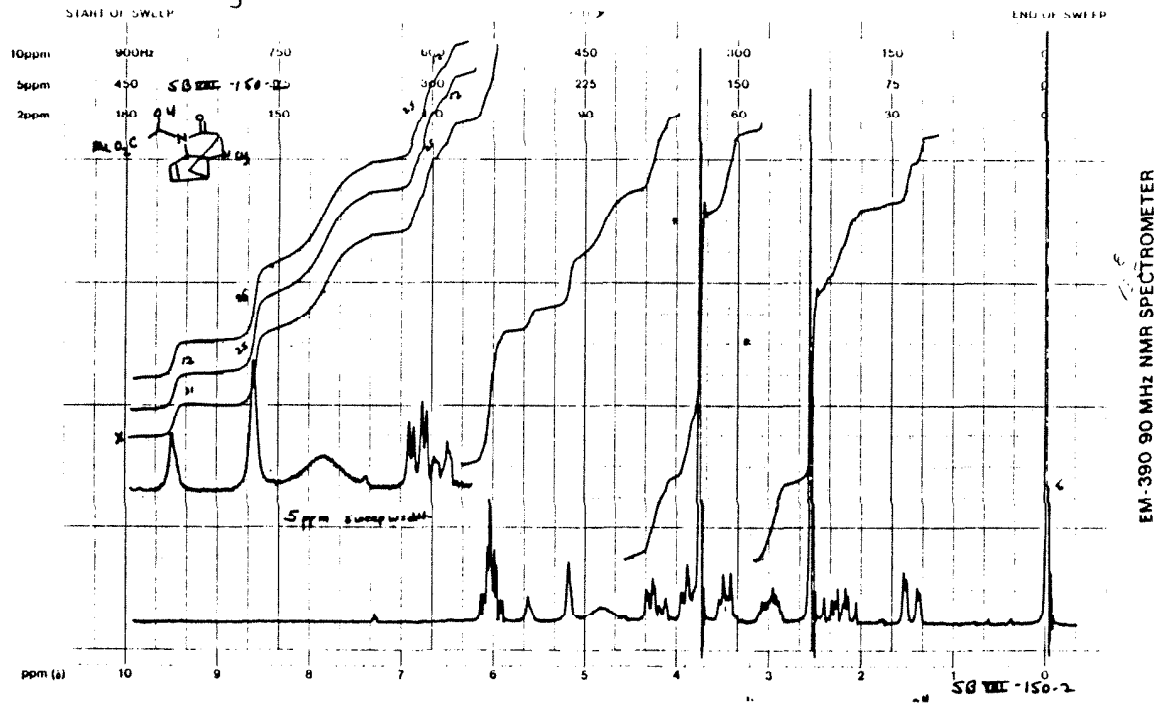
IR ($CHCl_3$)



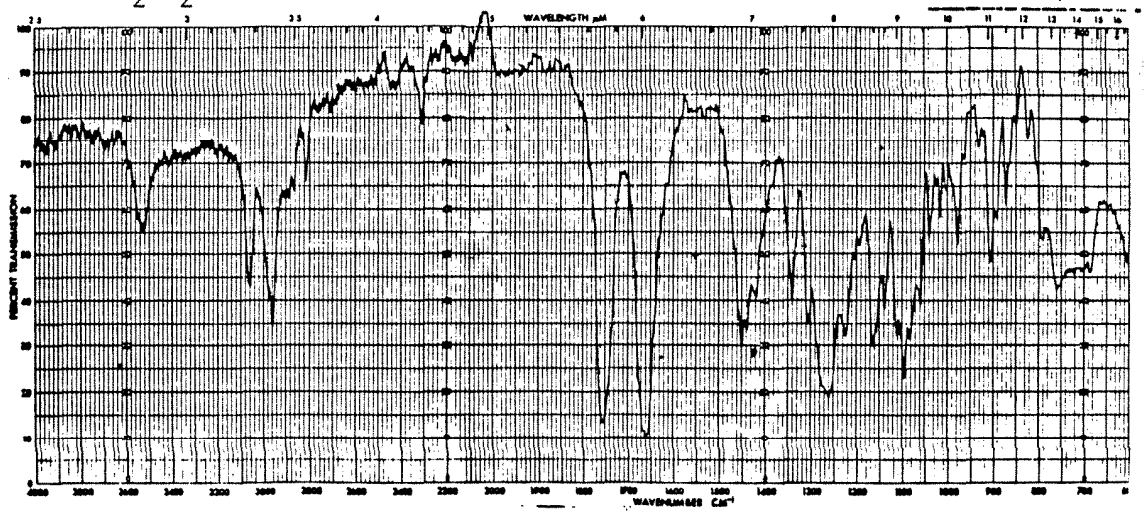


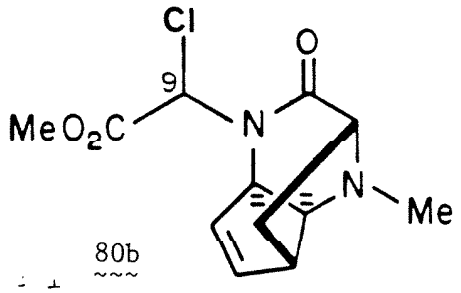
80a

^1H NMR ($CDCl_3$)



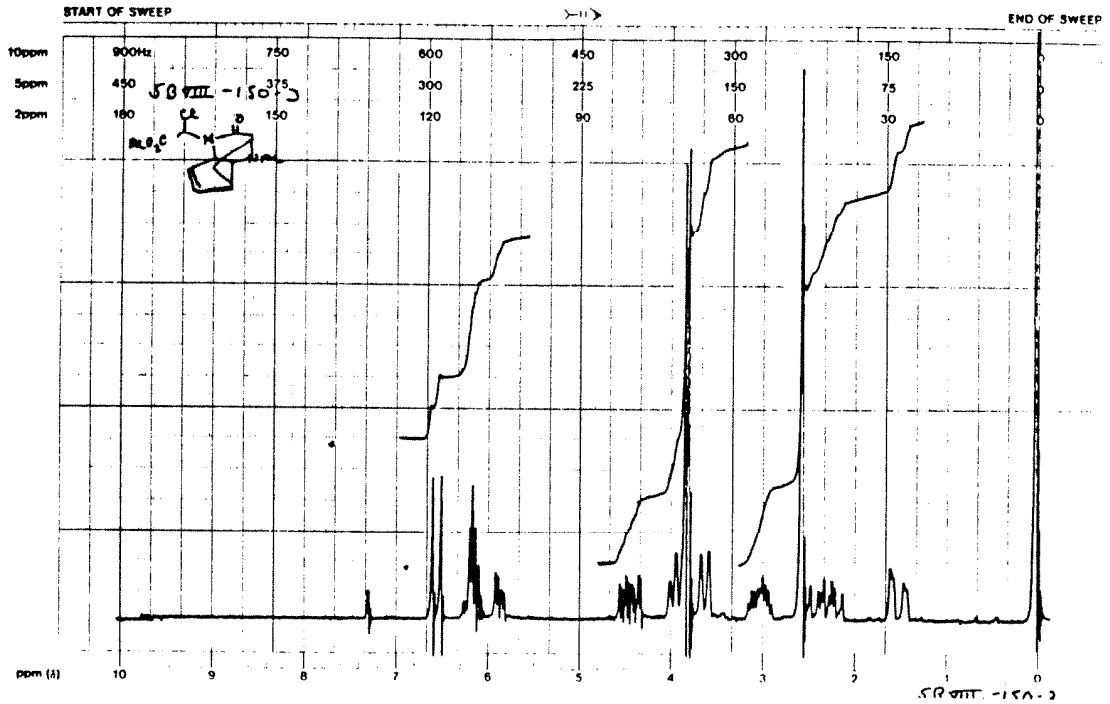
IR (CH_2Cl_2)



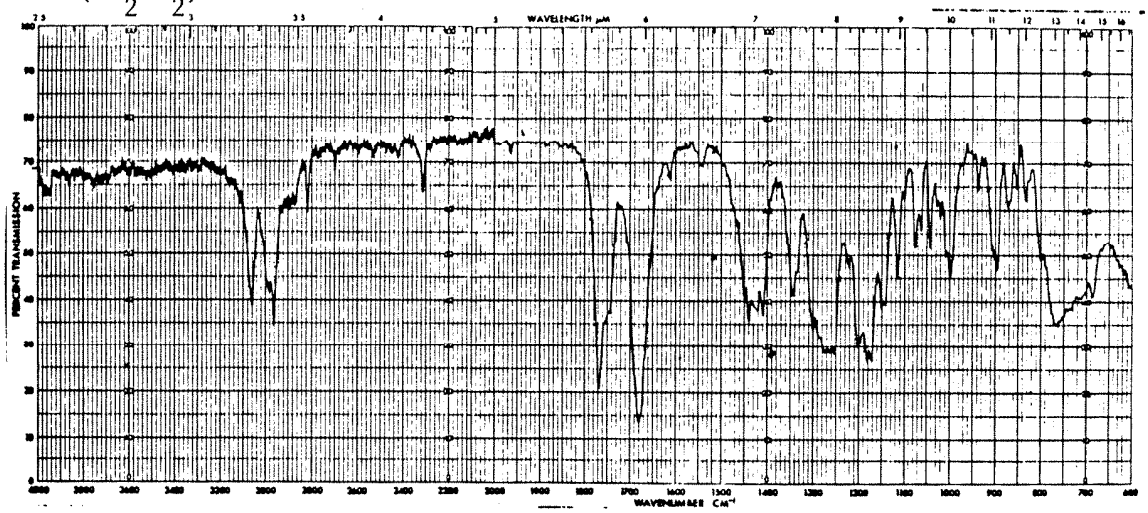


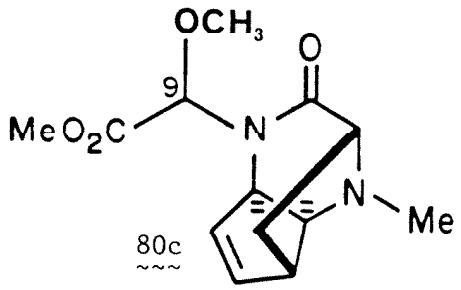
80b

^{1}H NMR ($CDCl_3$)



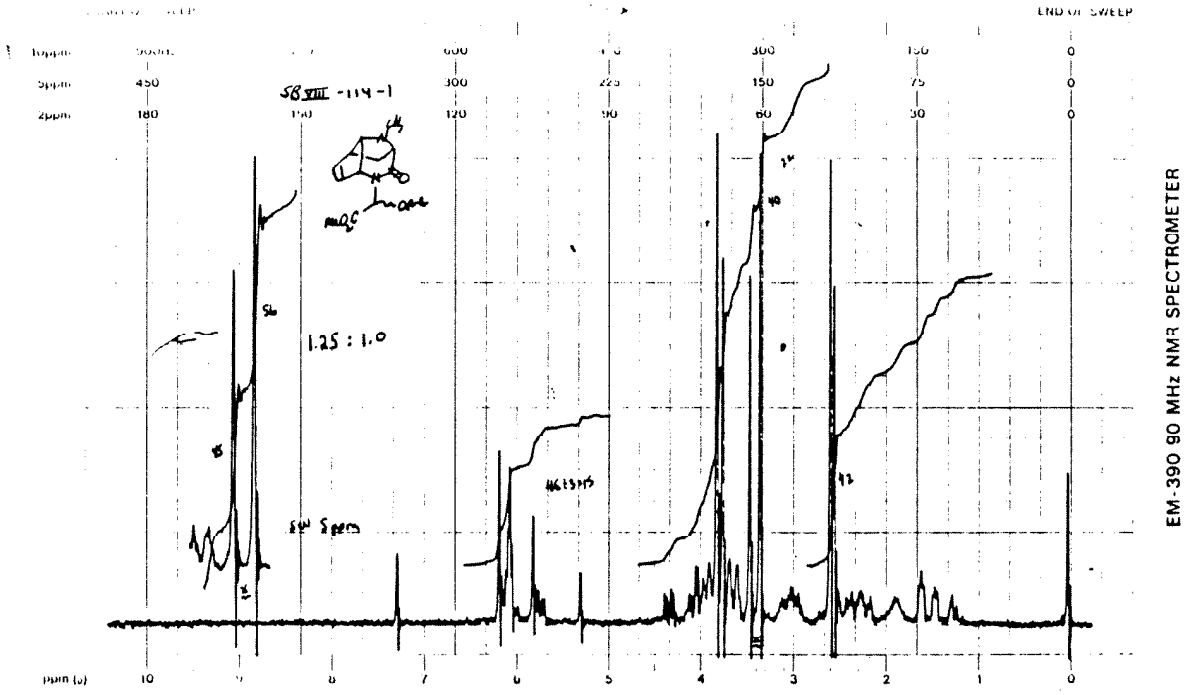
1R (CH_2Cl_2)



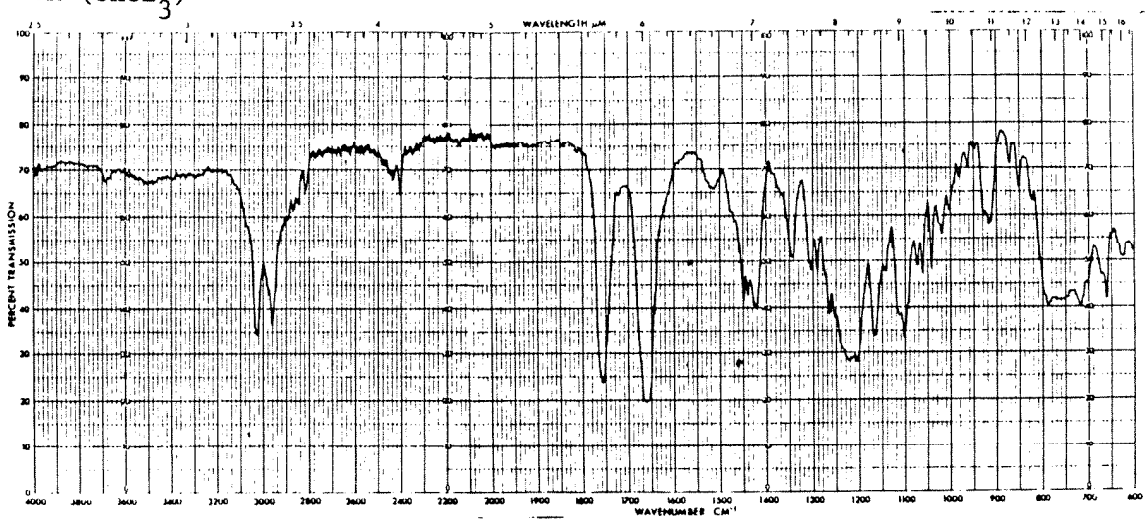


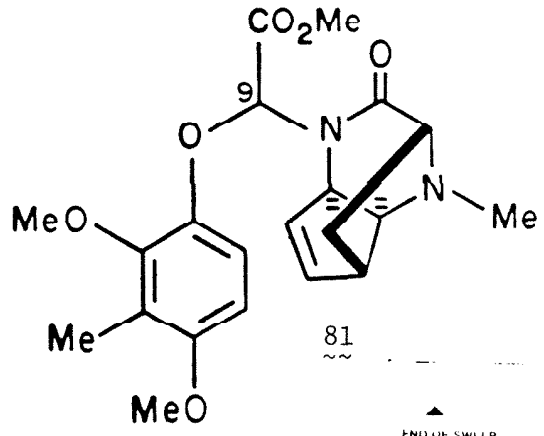
80c

^{1}H NMR ($CDCl_3$)



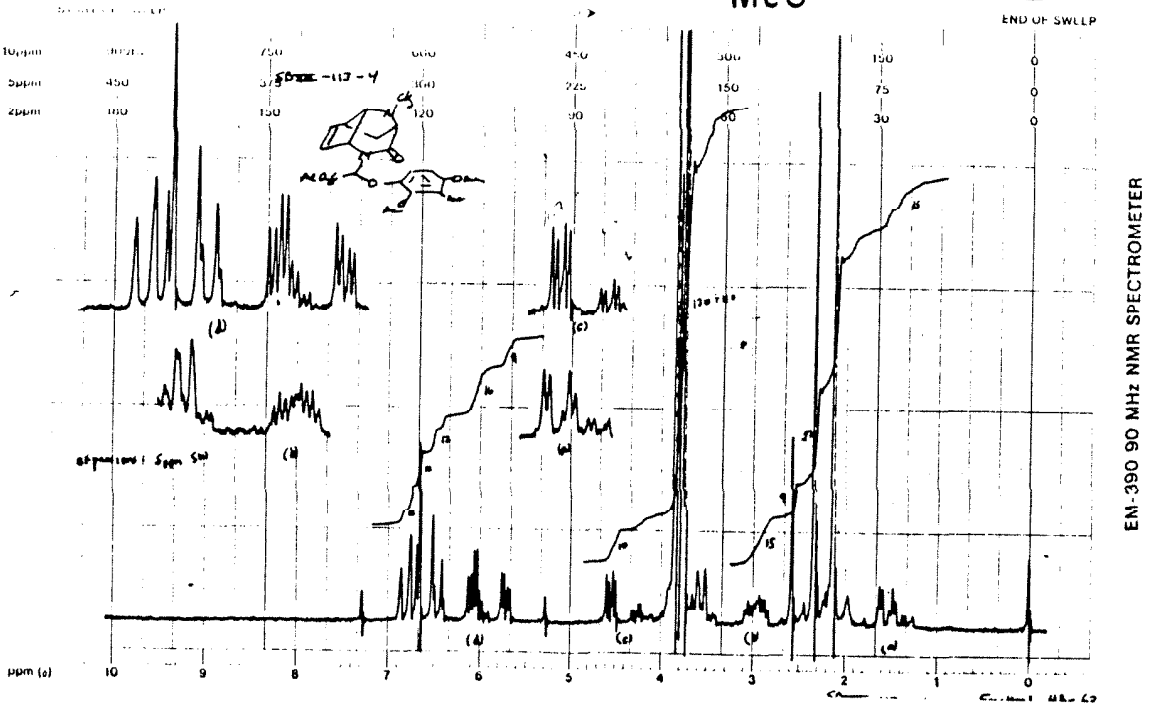
IR ($CHCl_3$)



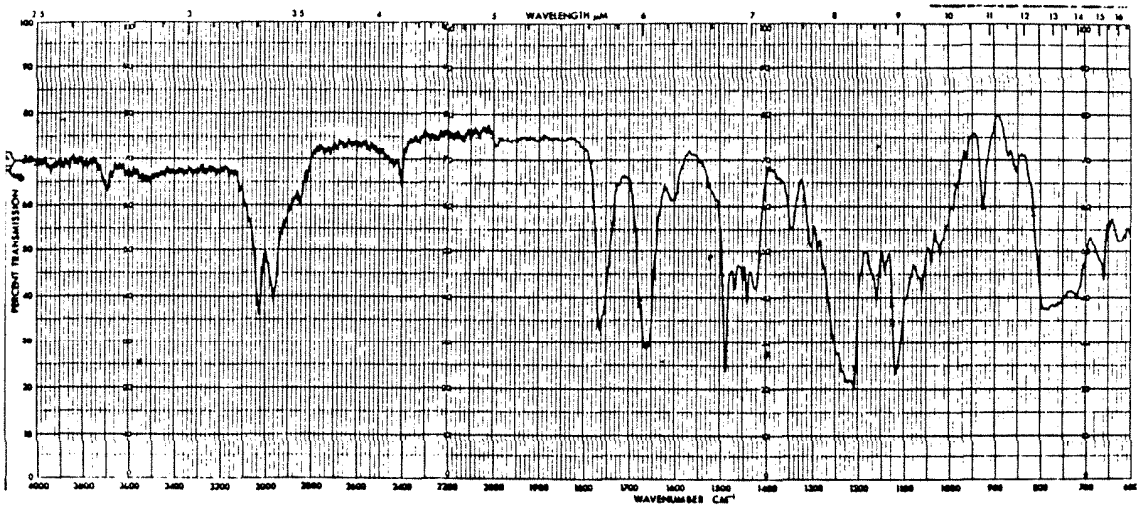


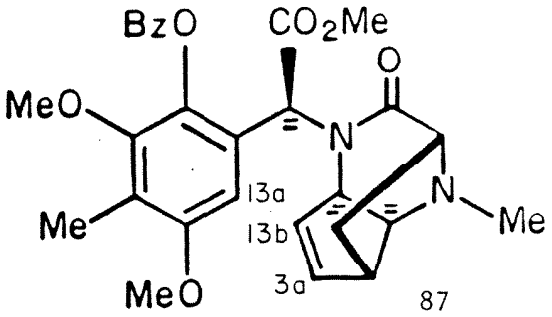
81

^{1}H NMR ($CDCl_3$)



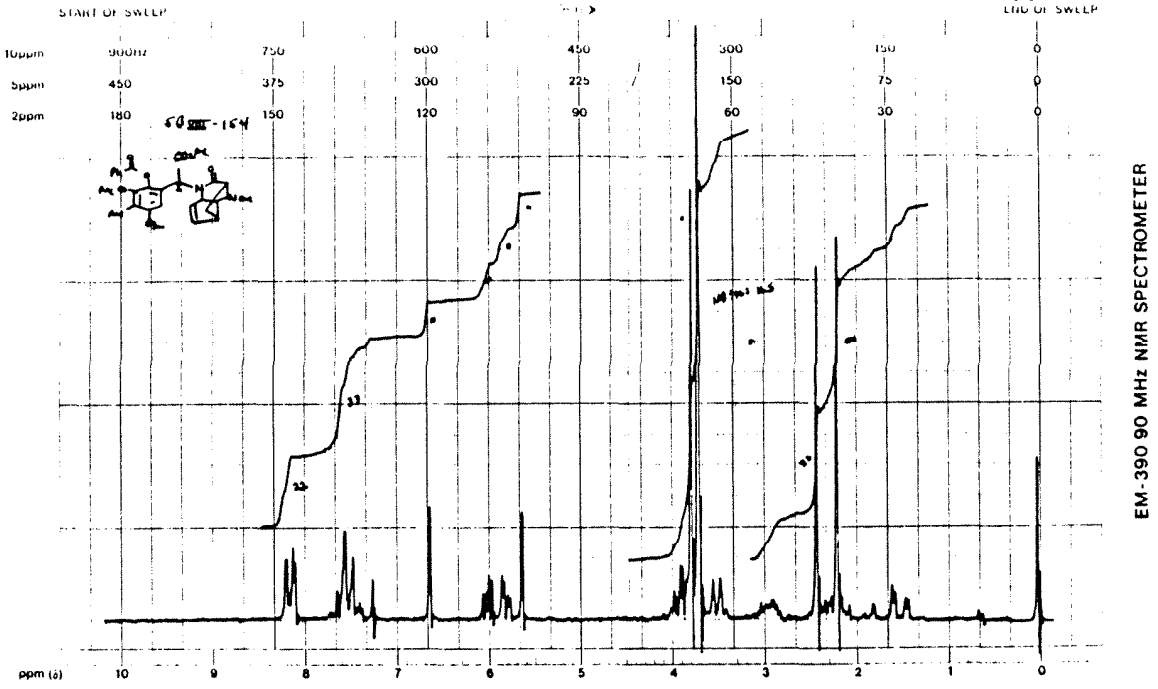
IR ($CHCl_3$)



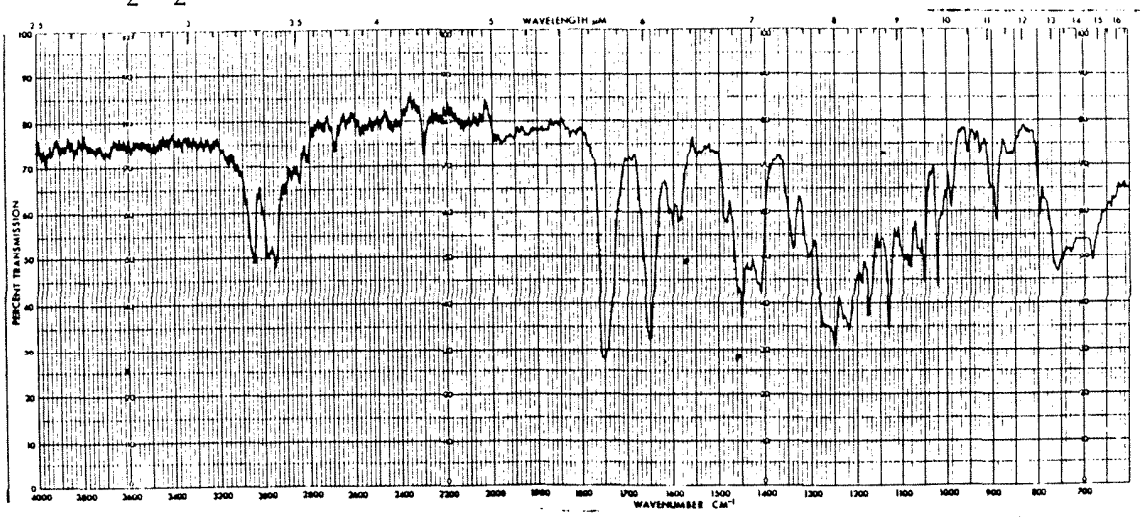


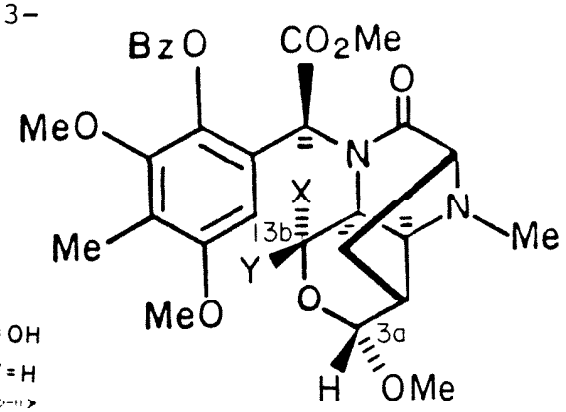
87

^{1}H NMR ($CDCl_3$)



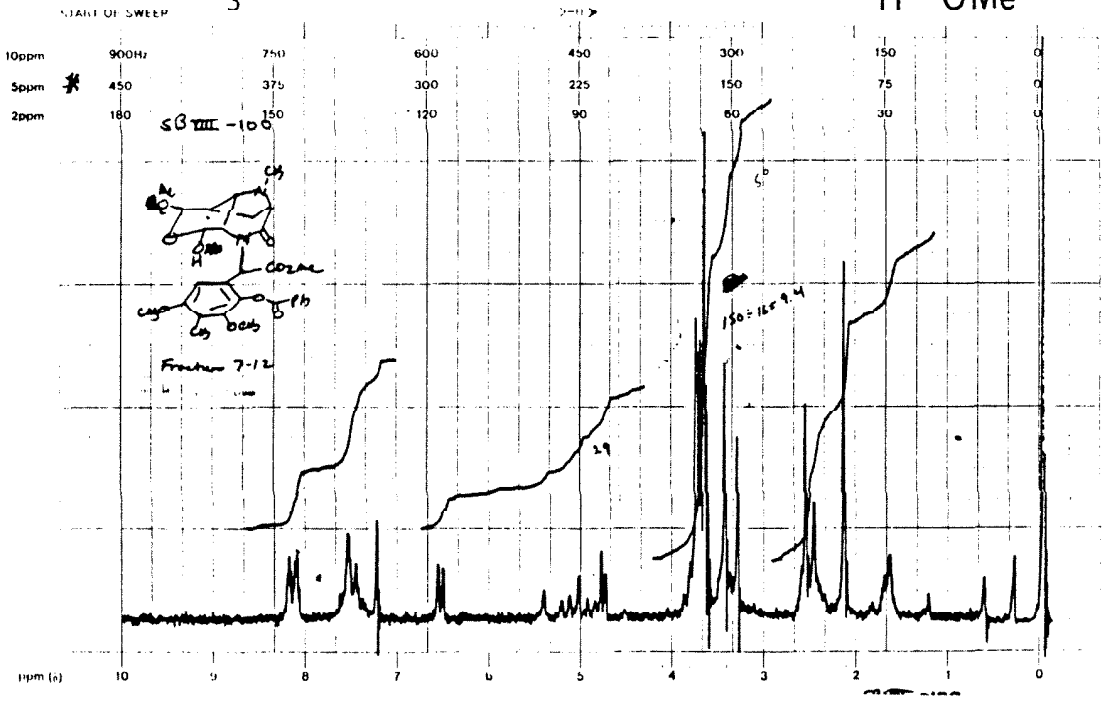
1R (CH_2Cl_2)



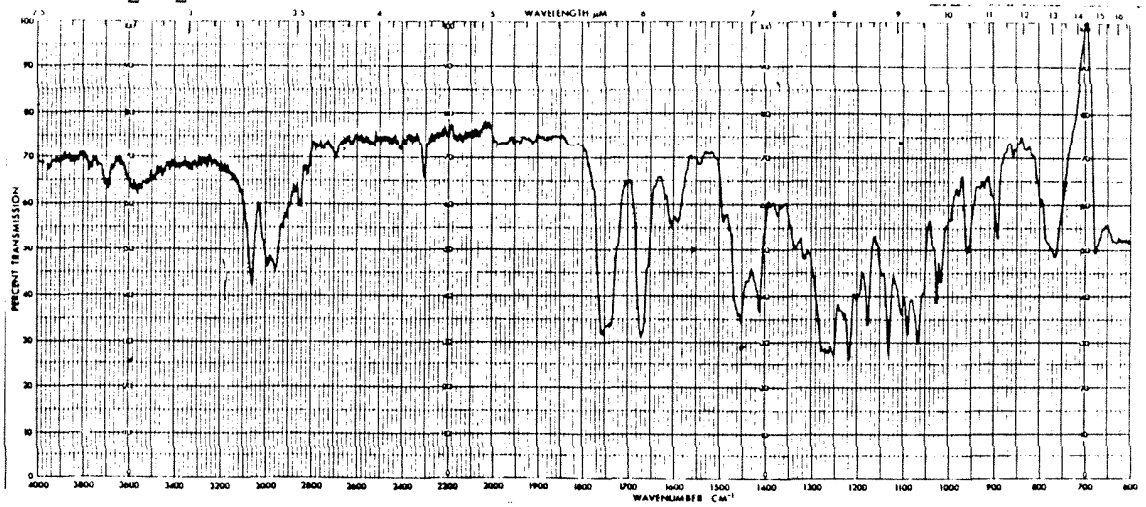


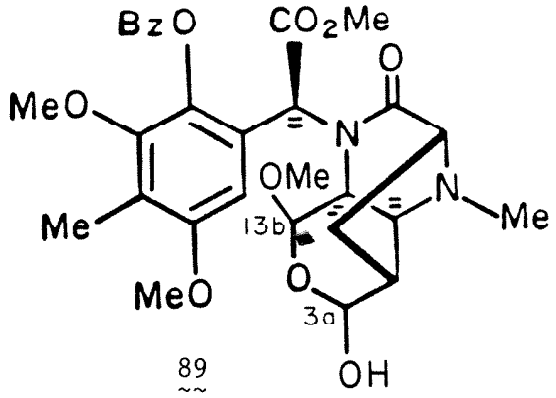
88 **a** X = H, Y = OH
~~ **b** X = OH, Y = H

^{1}H NMR ($CDCl_3$)



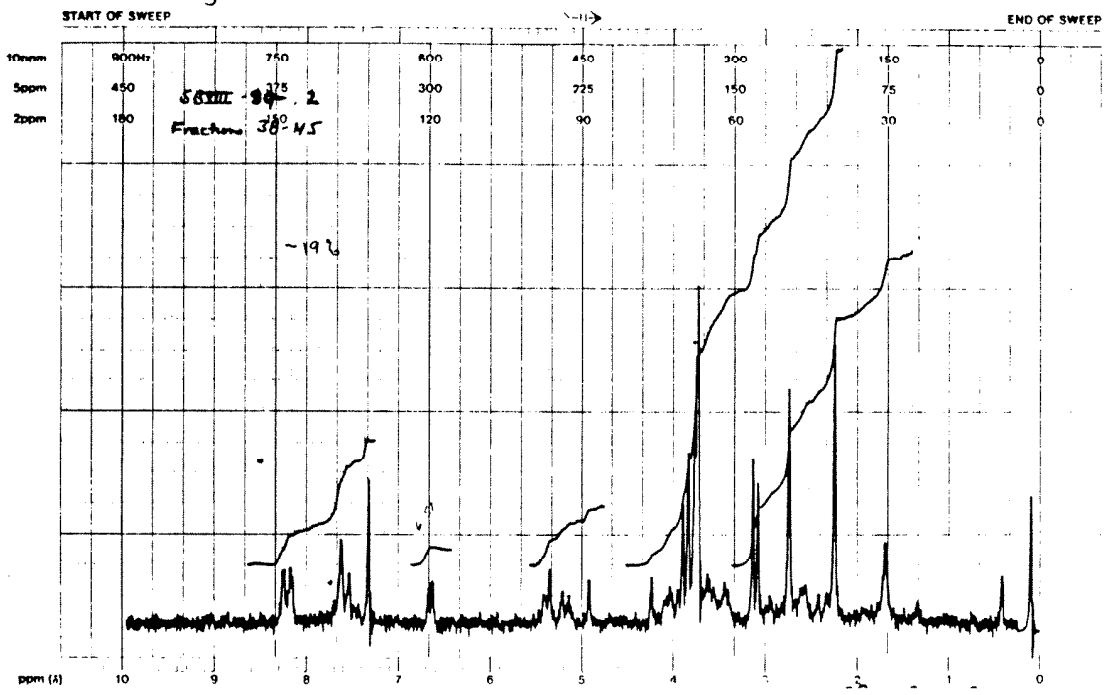
IR (CH_2Cl_2)

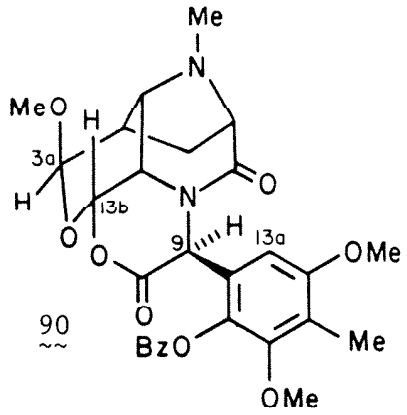




89

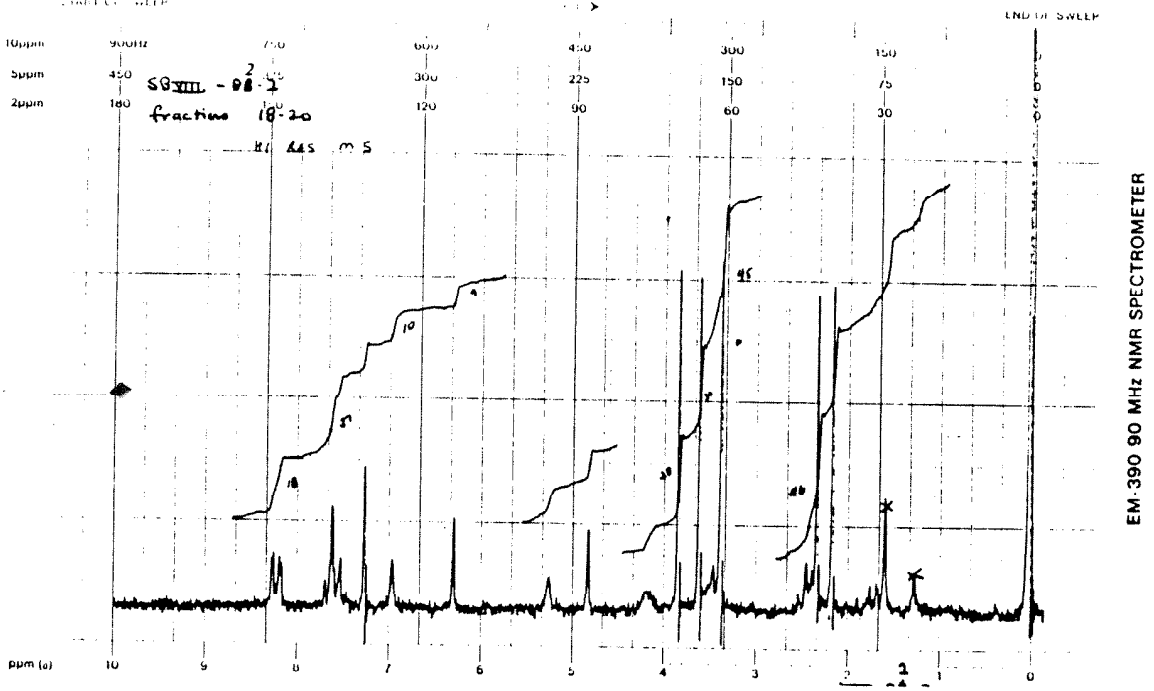
^{1}H NMR ($CDCl_3$)



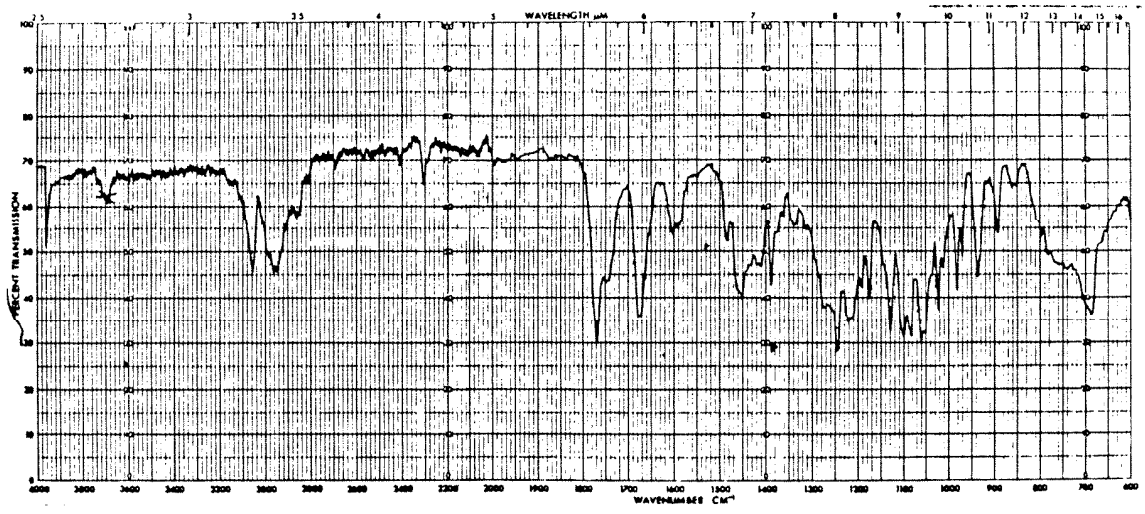


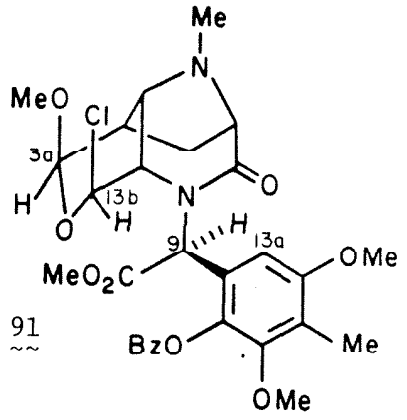
90

^{1}H NMR ($CDCl_3$)



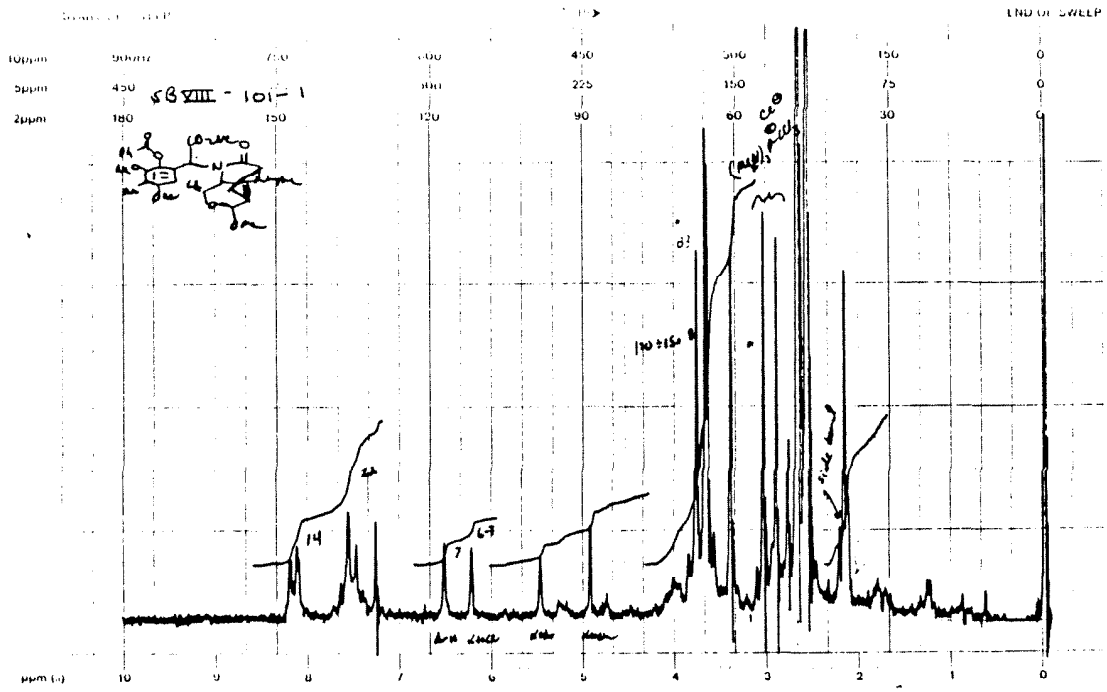
IR (CH_2Cl_2)

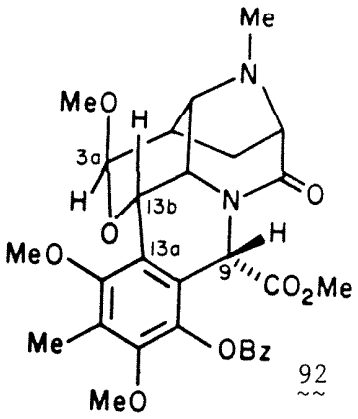




91

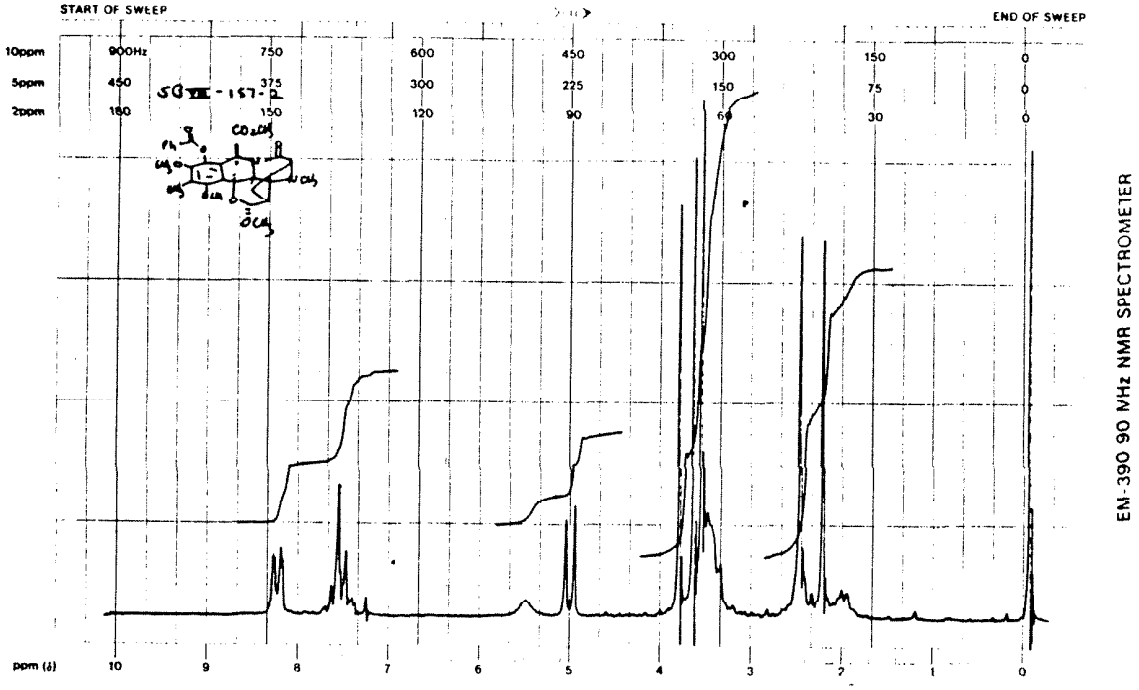
^{1}H NMR ($CDCl_3$)



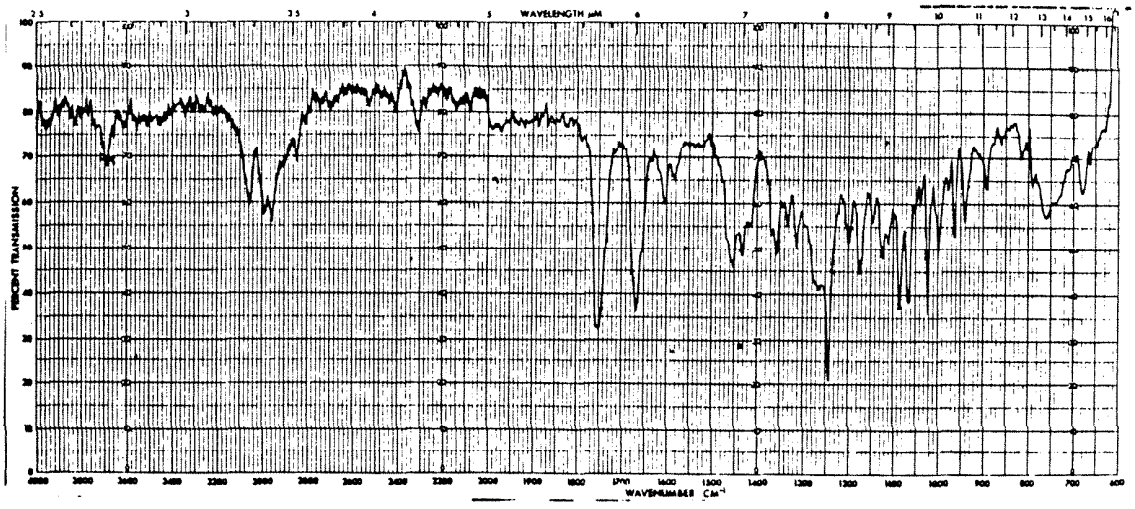


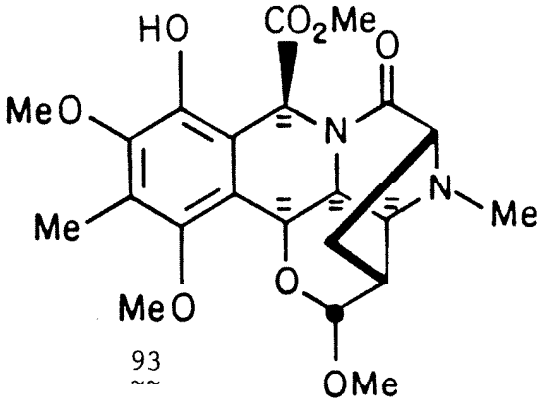
92

^{1}H NMR ($CDCl_3$)



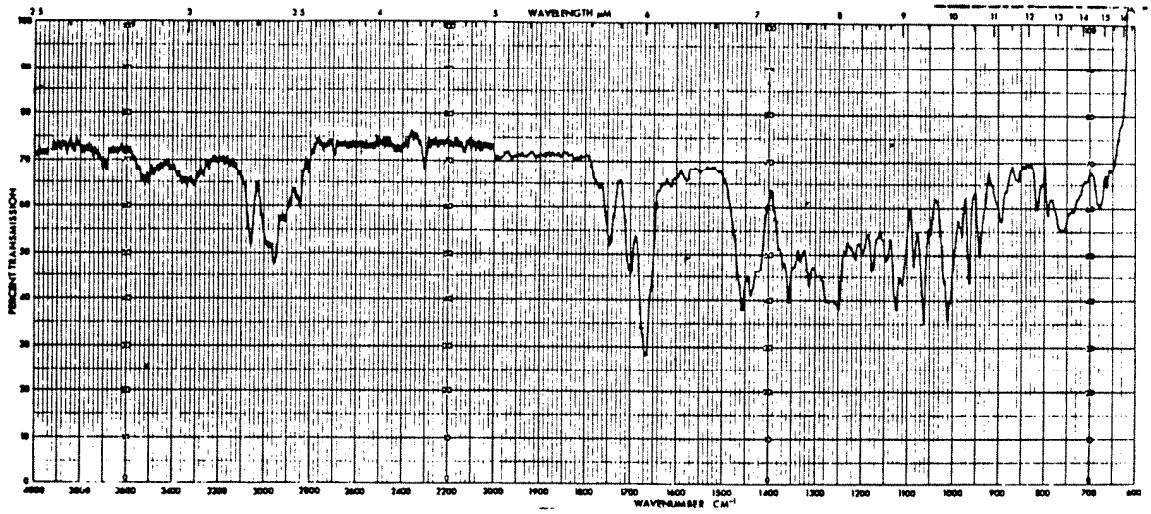
1R (CH_2Cl_2)



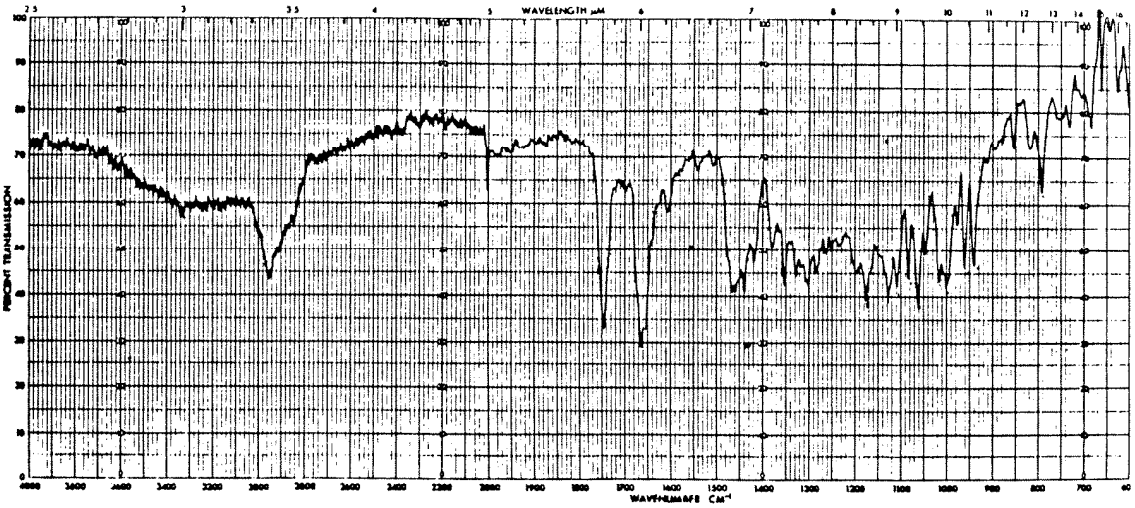


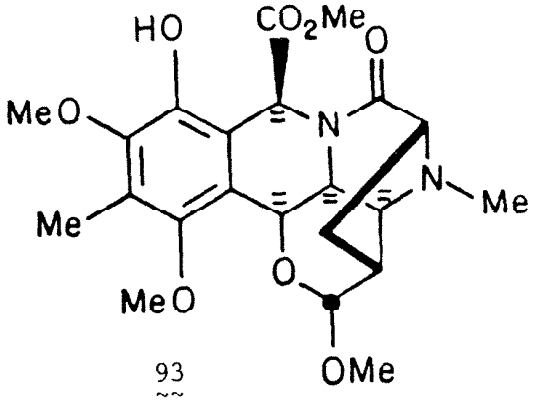
93

IR (CH_2Cl_2)



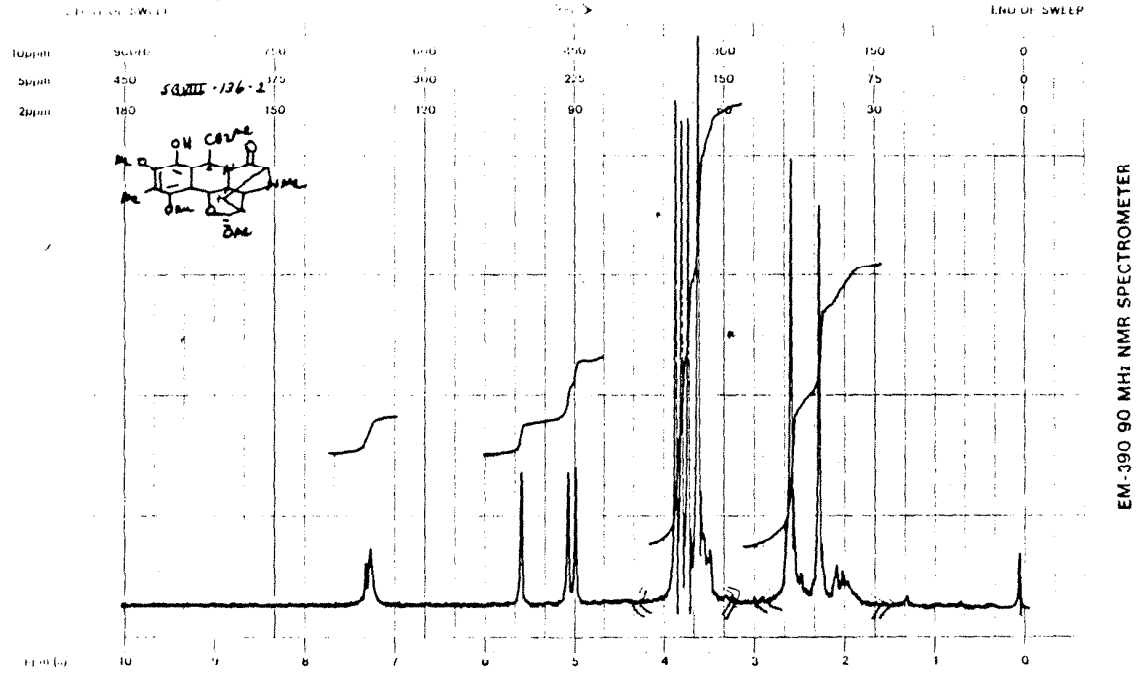
IR (neat)

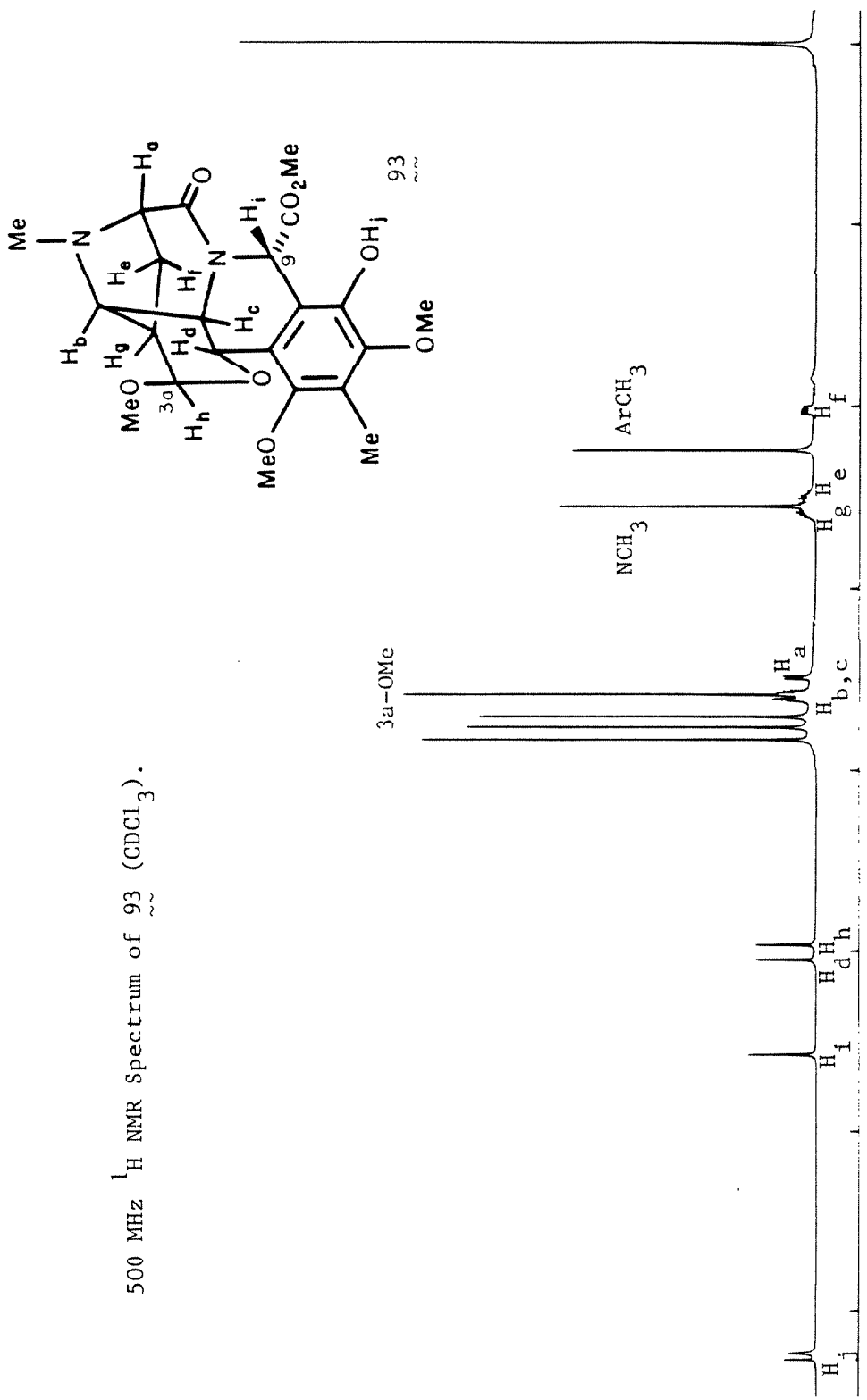




93

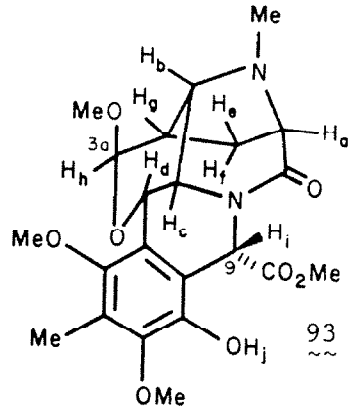
^{1}H NMR ($CDCl_3$)





500 MHz ^1H NMR Spectrum of 93 ($CDCl_3$).

500 MHz ^{1}H NMR Spectrum of 93: Expansions.



93